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FATTY LIVER OF ENDOCRINE ORIGIN

WITH SPECIAL REFERENCE TO FATTY LIVER OF MALNOURISHED AFRICAN INFANTS

BY

JOSEPH GILLMAN, D.Sc., M.B. AND CHRISTINE GILBERT, D.Sc.

Departments of Physiology and Anatomy, and the Joint Nutrition Research Unit of the C.S.I.R., and of the University of the Witwatersrand, Johannesburg

Fatty liver is one of the constant features of African infants suffering from pellagra and kwashiorkor (Gillman and Gillman, 1945). A mildly fatty liver containing approximately 8% of total lipids early in the illness may evolve into one containing over 40% of total lipids within nine days (Gillman and Gillman, 1951). Such a rapid evolution of the fatty change suggested that the acute episode in infants was the result of a sudden metabolic disorder occurring against a background of chronic malnutrition. This view implies that there are two stages in the natural history of florid kwashiorkor and infantile pellagra. The first, determined by chronic malnutrition, is initiated before or soon after weaning. No fatty liver develops during this stage, but the reactivity of the infant is altered, with the result that a mild intercurrent infection, a sudden change in temperature, or a mild gastro-intestinal upset may precipitate the second stage, which declares itself as florid kwashiorkor or as infantile pellagra. During the second stage a fatty liver develops rapidly. According to Davies (1948) and Trowell *et al.* (1954), this fatty liver is possibly due to "an almost complete suppression of the pancreatic enzymes from the gut."

The present experimental study was undertaken to ascertain whether a fatty liver of endocrine origin to be described in the baboon was in any way relevant to the mechanism concerned with the rapid development of a fatty liver of infants suffering from a florid form of infantile pellagra or kwashiorkor. It will be our purpose (1) to emphasize the importance of insulin, cortisone, and also of thyroxine in the pathogenesis of hepatic steatosis; (2) to demonstrate that in the presence of adequate thyroxine the mobilization of fat, even when excessive, will not result in a fatty liver; and (3) to suggest that the fatty liver of malnourished African infants is dependent not so much on the atrophy of the exocrine part of the pancreas as on the emergence of a particular endocrine physiology, the overall effect being a relative adrenocortical hyperactivity, accompanied by a relative or absolute depression of insulin.

Material and Methods

Twelve male and 17 female baboons were used in the present investigation. Nine male baboons were totally pancreatectomized, and thereafter the diabetes was controlled with long-acting insulin (Boots N.P.H.) which was administered twice daily, in the early morning and late afternoon. The morning urine sample was tested daily for its sugar content and twice weekly a check was kept on the resting blood sugar. In this manner the insulin requirements of each baboon were established. The maintenance dose of insulin ranged from 24 to 48 units daily and was not related proportionally to the body weight of the baboon. Four of the depancreatized male baboons were totally hypophysectomized at intervals of 4 to 15 months after removal of the pancreas, the operation being performed according to the method of Dr. E. Epstein (to be published).

Three male and 10 female baboons were totally thyroidectomized. An additional five female baboons were hypophysectomized, while in the remaining two the stalk of the pituitary gland was sectioned. The latter was effected by inserting a platinum plate between the pituitary and the diaphragma sellae, thereby excluding any possibility of a vascular connexion being re-established between the pituitary and the hypothalamus.

Cortisone was administered on a body weight basis—namely, 1 mg./kg. body weight/day, the injection being given in two divided doses. Except where stated otherwise, the dosage of thyroxine was the same for all the baboons—namely, 0.5 mg. three times weekly.

Experimental

Hypophysectomy.—Fat failed to develop in the livers of any of the four baboons during an eight-months period following hypophysectomy.

Thyroidectomy.—Complete thyroidectomy of male and female baboons was not associated with the development of a fatty liver even when observed over a four-year period. In this respect the baboon behaved differently from the dog (Chaikoff *et al.*, 1948).

Pancreatectomy and Fatty Liver

Total pancreatectomy was performed on nine male baboons ranging in age from 3 to 5 years. The small fragments of pancreas which usually adhere closely to the duct and extend into the wall of the duodenum were carefully dissected away, but the duodenum itself was left intact. Within six hours after the operation the blood sugar rose to between 200 and 350 mg. per 100 ml., and the baboons became dependent on insulin for the control of the diabetes. Appetite, and the preferences displayed by some baboons for vegetables, and by others for the prepared ration (Gillman and Gilbert, 1956f), influenced, but did not alone determine, the insulin requirements of the individual baboon.

Experience disclosed that if fatalities were to be avoided it was undesirable to cause the blood sugar to fall too low during the night. Only a small amount of long-acting insulin was administered in the evening, with the result that in all the pancreatectomized baboons the morning sample of urine contained sugar, while the resting blood sugar was raised to between 170 and 400 mg. per 100 ml. Although the diabetes was controlled during the day, it was not entirely controlled for a period of approximately 8 to 10 hours during the night. If these facts are borne in mind, it is now possible to examine the effects of pancreatectomy on the fat content of the liver.

Under the conditions of our experiments, some fat is frequently, but not invariably, found in the livers of insulin-treated, depancreatized baboons. The amount of fat in the liver is a function of the efficiency of the control of the diabetes rather than of the lack of some pancreatic factor other than insulin, as seems to be the case in the dog. Where we have attempted to control the diabetes effectively by giving increased amounts of insulin during the day and night, histologically visible fat can be removed completely from the liver. Even where the diabetes is less well controlled and fine droplets of fat are present in the cells of the periportal region, the total fat content of the liver does not exceed 8%. The latter represents only a small increase above control values and cannot be compared with the much greater accumulation of the fat reported by Prohaska *et al.* (1936), Dragstedt *et al.* (1936), and Chaikoff *et al.* (1947) in insulin-treated depancreatized dogs.

Lipocaic, free choline, methionine, or pancreatic enzymes are apparently not required by the depancreatized baboon as they are by the dog. Possibly the gut of the baboon elaborates a substance akin to lipocaic or may compensate for the loss of pancreatic enzymes by some other mechanism still to be elucidated. Length of survival after pancreatectomy does not influence the fat content of the liver. Baboons surviving for 18 months do not show any progressive increase in liver fat. These results disclose that, so far as the baboon is concerned, the exocrine part of the pancreas does not influence appreciably the presence or absence of fat in the liver.

The withdrawal of insulin from depancreatized baboons is followed sooner or later by grave constitutional signs, although most animals can tolerate an insulin-free period of four to five days. Without exception, the fat content of the liver increases rapidly in every baboon after withdrawal of insulin. Chemical estimations disclosed a fat content of over 40% of the wet weight of the liver.

Within 48 hours after the withdrawal of insulin from depancreatized baboons the liver cell fills rapidly with discrete globules of fat which are distributed throughout the lobule. Although at first the fat seems to be more abundant in the periportal region than elsewhere, this localization becomes less apparent as fat accumulates in all the cells of the lobule. A striking and consistent feature is the discrete nature of the fat globules which fill the enlarged cell. The globules may later fuse to form a single large fat droplet occupying the greater part of the cytoplasm, emphasizing the similarity of structure between the fatty liver of malnourished infants and that of the insulin-deprived depancreatized baboon. As the fat accumulates in the baboon's liver the glycogen disappears until eventually only histochemically detectable glycogen is to be found in the large, vacuolated nuclei.

As soon as insulin therapy is begun the lipaemia, ketosis, and hyperglycaemia subside rapidly—that is, within four to six days—while two weeks may elapse before the liver fat is reduced to levels comparable to those prevailing prior to the withdrawal of insulin. The fat seems to disappear first from the mid-zone, and for a while remains localized to the central and peripheral parts of the lobule. Later the fat disappears for the most part from the central zone and is then confined to the periportal region for several weeks, the precise time depending on the degree of control of the diabetes. The remarkable accumulation of fat in the liver of the insulin-deprived depancreatized baboon and the reduction in fat after the control of the diabetes emphasize the crucial role of insulin in regulating the amount of fat in the liver of depancreatized baboons.

Effect of Hypophysectomy on Fatty Liver of Depancreatized Baboons

Since the absence of insulin from depancreatized baboons promotes the rapid movement of large amounts of fat into the liver, it remained to be determined whether this movement of the fat was due to the unantagonized effect of other hormones, the secretion of which was immediately regulated by the pituitary gland, or was entirely a function of insulin alone.

The pituitary gland was removed completely from four depancreatized baboons. The animals remained in good condition after the operation, and one animal showed marked clinical improvement after hypophysectomy. In all cases the insulin requirements were reduced to one-third or one-quarter of the prehypophysectomy levels.

When deprived of insulin, the blood sugar of the depancreatized-hypophysectomized (D.-H.) baboons continues to rise and the glycosuria becomes intense, the urine containing over 2 g. of sugar per 100 ml. The severe lipaemia and the ketosis are prevented, but the phospholipids and the total cholesterol may continue to rise to near prehypophysectomy levels. It is thus evident that, while the disorder of carbohydrate metabolism has not been alleviated in depancreatized baboons after removal of the pituitary, the rise in the triglyceride component of the blood fats has been suppressed (Gillman *et al.*, 1957a).

The small amount of fat present in the liver of the depancreatized insulin-treated baboon may persist after hypophysectomy and for as long as insulin is administered. Insulin withdrawal, however, is not followed by the accumulation of fat in the liver, and the little fat present before withdrawal may disappear completely. In other words, the fatty liver fails to develop in insulin-deprived D.-H. baboons even at the end of nine days. During this prolonged period of insulin withdrawal the baboons remain clinically well, in contrast to depancreatized baboons, which, as mentioned above, may show marked constitutional reactions if deprived of insulin for four to five days.

These findings in the four D.-H. baboons indicated that the fatty liver of the depancreatized baboon was due not only to a lack of insulin but also to the activity of other endocrine glands immediately regulated by the hypophysis. An opportunity thus became available for assessing the importance of the adrenal gland and of the thyroid in the genesis of a fatty liver.

Effect of Cortisone and of Thyroxine on Liver Fat in D.-H. Baboons

Two D.-H. baboons on insulin therapy received a 23-day course of treatment with cortisone. Withdrawal of insulin during the period of cortisone treatment was associated with a return of the intense lipaemia, but was unaccompanied by ketosis. The liver became fatty once again, although the estimated amount of fat was approximately half that observed in the same animal during an insulin-withdrawal period before hypophysectomy. The administration of insulin to the D.-H. baboons receiving cortisone promptly led to resorption of the fat. If, thereafter, thyroxine was injected every second day in conjunction with cortisone for 15 days, the withdrawal of insulin was rapidly followed by a fatty liver as intense as that observed in the insulin-deprived depancreatized baboon.

The administration of thyroxine alone for 21 days to two D.-H. baboons did not produce a fatty liver in the absence of insulin.

Two insulin-treated D.-H. baboons received cortisone for 53 days, and then thyroxine as well for a further 32 days. The cortisone and thyroxine were withdrawn, but the insulin was continued for another 14 days. Thereafter the

insulin treatment was stopped for six days, at which time another liver biopsy was taken. The histological section revealed the presence of abundant liver fat, indicating that even 14 days after withdrawal cortisone was still active in the baboon.

In short, these experiments in the D.-H. baboons indicated that, in the absence of insulin, cortisone alone could promote a moderately fatty liver which could be intensified by thyroxine, leading to a picture indistinguishable from the liver of a depancreatized baboon deprived of insulin. Cortisone continues to assert itself in the baboon at least 14 days after the last injection.

We should add that we failed to produce a fatty liver in a single depancreatized baboon receiving insulin after the administration of bovine growth hormone in amounts shown by Campbell *et al.* (1953) to produce an intensely fatty liver in dogs. In view of the controversy about the species specificity of growing hormone, we hesitate to attach any importance to a single observation in the baboon. But our experiments disclose that at least one kind of fatty liver can be produced without growth hormone or adipokinin.

Effect of Cortisone, Thyroxine, and Cortisone and Thyroxine in Hypophysectomized and Stalk-sectioned Baboons

Cortisone

Five hypophysectomized female baboons and two stalk-sectioned baboons received cortisone daily for 26 to 180 days. Serial biopsies of the liver disclosed that cortisone treatment for 56 days was unassociated with the development of any fat in the liver. When continued for 93 days the liver became moderately fatty, large globules of fat occupying the cells of the outer half of the lobule, and much smaller droplets the central region. At the end of 180 days the liver was intensely fatty and resembled that of the depancreatized baboons not receiving insulin.

Prolonged treatment with cortisone also resulted in a progressive increase in round cells and a substantial thickening of the portal tracts as well as of the reticulin of the related sinusoids. Moreover, in one hypophysectomized baboon an occasional vacuolated nucleus, similar to those described in depancreatized insulin-deprived baboons, was observed in the liver cells bordering the portal tracts. The blood sugar was not elevated in the cortisone-treated hypophysectomized baboons, although the resistance to insulin was increased and there was evidence of some intolerance to glucose as reflected by the intravenous glucose test (unpublished data).

As we were interested in defining the conditions promoting oestrogen-withdrawal bleeding in hypophysectomized baboons (Gilbert and Gillman, 1956, 1957), we had occasion to pretreat two baboons with cortisone for 26 and 44 days respectively, and then to subject them to a further course of cortisone in conjunction with oestrogen (0.1 mg. of oestradiol benzoate daily), the oestrogen being withdrawn after 14 days but the cortisone continued. Pretreatment with cortisone, followed by simultaneous injections of oestrogen and cortisone, led to the accumulation of fine droplets of fat throughout the lobule, with coarse globules concentrated in the liver cells in the periportal sector. The course of treatment with oestradiol benzoate thus appeared to accelerate the accumulation of fat in the liver of hypophysectomized baboons receiving cortisone therapy.

In this connexion it should be mentioned that a course of treatment with corticotrophin (1 unit/kg. body weight/day) for 46 days, followed by corticotrophin and oestradiol benzoate for 13 days, resulted in a fatty liver even more severe than that produced by cortisone and oestradiol benzoate mentioned above. Again the fat was concentrated chiefly in cells of the outer half of the lobule.

It is thus apparent that cortisone alone, in the concentrations used, will promote a fatty liver in hypophysectomized baboons if treatment is continued for longer than 93 days. If the fat in the liver is derived from the depots, then the liver can cope with the increased load for an extended period of time. Moreover, the speed of development of the fatty liver in hypophysectomized baboons receiving cortisone or corticotrophin can be accelerated by the administration of oestradiol benzoate.

Two baboons which had received daily cortisone therapy for 126 and 200 days respectively and showed an intensely fatty liver on biopsy were thereafter subjected to a 14-day course of treatment with thyroxine in conjunction with the cortisone. At the end of 14 days the fat content of the liver was sharply reduced. During this short period of time, therefore, thyroxine initiated a rapid decline in the fat content of the liver.

Thyroxine

Thyroxine (0.2 mg./2nd day) was administered to three hypophysectomized baboons and to one stalk-sectioned baboon for 21 to 28 days respectively. All the animals lost weight, and, in view of the severe constitutional disturbances in the hypophysectomized baboons, the treatment could not be continued for a longer period. Fine particles of fat were found in the cells throughout the liver lobule, but, unlike the cortisone-treated hypophysectomized animals, the fat was localized almost exclusively in the sinusoidal pole of the cell.

Cortisone and Thyroxine

Three hypophysectomized baboons and two stalk-sectioned baboons received cortisone daily for a minimum of 56 days, followed by the simultaneous administration of cortisone and thyroxine for a further 38 days. Cortisone treatment was therefore administered uninterruptedly for a minimum period of 94 days. Biopsy of the livers of the baboons at the end of treatment with both hormones showed the presence of fine fat particles in the liver cells throughout the lobule.

The simultaneous withdrawal of cortisone and thyroxine was followed by a steady increase in the fat content of the liver cells. By the 13th day the fat particles were larger, and by the 27th day had coalesced to form large globules, completely filling the cell. The liver then presented a picture indistinguishable from the severely fatty liver of malnourished infants. In fact, this type of fatty liver was more severe than any other thus far produced experimentally in baboons.

Death supervened in three animals within 25 to 99 days after the withdrawal of cortisone and thyroxine.

It should be mentioned that during an earlier experiment one baboon received a 41-day course of treatment with cortisone followed by 38 days' treatment with cortisone and thyroxine. The total period of cortisone treatment was therefore 79 days. The simultaneous withdrawal of cortisone and thyroxine in this baboon was not followed by the development of a fatty liver even at the end of 45 days. On a subsequent occasion, when the baboon had received cortisone uninterruptedly for 162 days, including the terminal 36 days of therapy with cortisone as well as thyroxine, the simultaneous withdrawal of both hormones was followed by the development of a severely fatty liver and death within 26 days. These two experiments in the same baboon indicate that the total length of treatment with cortisone is important for the production of an intensely fatty liver following the withdrawal of cortisone and thyroxine. The fatal outcome of this kind of fatty liver, despite all kinds of treatment, including the intragastric feeding with protein-enriched diets, is to be stressed, and is reminiscent of that which obtains in malnourished infants also suffering from a fatty liver of similar intensity. Not the malnutrition but the severe metabolic disorder is immediately responsible for death.

Discussion

Depancreatized baboons deprived of insulin for several days, like other mammals in similar circumstances, accumulate large amounts of fat in the liver. In cats

(Long and Lukens, 1936), as in baboons, this kind of fatty liver can be prevented by the removal of the hypophysis. Since cortisone promotes a fatty liver in insulin-deprived D.-H. baboons, and since Long and Lukens have shown that the fatty liver fails to emerge in depancreatized, adrenalectomized, insulin-deprived cats, but does so after the injection of cortical extracts, it follows that in depancreatized cats and baboons deprived of insulin the pituitary, via its action on the adrenal cortex, is essential for the production of the fatty liver. In the case of D.-H. baboons, thyroxine potentiates the fat-promoting effect of cortisone. Evidently the fatty liver of depancreatized baboons is due not only to the lack of insulin but also to the presence of an adrenocortical hormone akin to cortisone and in amounts greater than that available in hypophysectomized baboons.

In the presence of adrenocortical activity and in the absence of insulin, the intensity of the fatty change in the liver is regulated by thyroxine. The fatty liver then is dependent on a dynamic relationship between insulin, adrenocortical hormone, and thyroxine. If this relationship is disturbed, such that insulin is relatively or absolutely decreased beyond a level still to be defined, fat will accumulate in the liver, whereas, if insulin is relatively increased, the fatty liver will be prevented. It is significant that the insulin requirements of D.-H. baboons are greater after cortisone therapy, and the fatty liver will be prevented only if the amount of insulin is increased.

Even in hypophysectomized or stalk-sectioned baboons the administration of sufficient cortisone for at least 90 days will so alter the insulin–adrenocortical relation that the liver will become moderately fatty. With the appearance of fat in the liver the blood lipids may also rise. These two events, taken in conjunction with the presence of occasional vacuolated nuclei in the liver cells near the portal tracts, of the kind previously reported in depancreatized baboons (Gillman and Gilbert, 1956a), more than suggest a relative or absolute deficiency of insulin.

During the process of continued fat synthesis and storage and with the expansion of the fat depots, consequent on prolonged treatment with cortisone, the baboon develops a measure of intolerance to glucose, acquired perhaps through the elaboration of an insulin inhibitor similar to that described by Bornstein (1953), or through the production of an alloxan-like substance (Loubatières, 1954). There is, however, no glycosuria, and the resting blood sugar is either normal or at most reaches the upper limits of normality.

It is unlikely that the pancreas is slowly exhausted of its insulin by cortisone, because the administration of large amounts of thyroxine to cortisone-treated hypophysectomized or stalk-sectioned baboons leads to a reduction in the blood lipid, mobilization, and oxidation of the depot fats with a sharp decrease in body weight. If the islets were exhausted, this increased metabolism, consequent on thyroxine administration, should still further emphasize the insulin deficit, but this does not happen. The cortisone-produced fatty liver of the hypophysectomized baboon, therefore, also seems to depend on an altered insulin–cortisone relationship.

The fatty liver consequent on cortisone–thyroxine withdrawal develops consistently in hypophysectomized or stalk-sectioned baboons treated with cortisone for a period of not less than 90 days, including the terminal 38 days during which thyroxine is also administered. Within 25 days after withdrawal of both hormones the liver is extremely fatty. Since little if any fat is present in the liver on the day of withdrawal of both hormones, even in circumstances where cortisone has been injected for 162 days and thyroxine for the terminal 60 days of the experiment, it is evident that thyroxine prevents the deposition of fat in the liver.

Significant, too, in this connexion is the observation that so long as thyroxine is administered the protein-bound iodine (P.B.I.) is raised, but soon after withdrawal of cortisone and thyroxine the P.B.I. drops rapidly to the very low levels found in hypophysectomized baboons (van Zyl, 1955). This reduction in P.B.I. coincides with the arrest of weight loss, and within a few days the fat accumulates rapidly in the liver.

The fatty liver of cortisone–thyroxine withdrawal therefore begins to emerge when the thyroxine has been metabolized. Since the effects of cortisone certainly persist in D.-H. baboons for 14 days and in hypophysectomized baboons for at least six to eight weeks after the last treatment, the fatty liver of cortisone–thyroxine withdrawal evidently develops when the amount of thyroxine is steadily decreasing and when cortisone is still asserting itself.

As long as thyroxine is available in adequate amounts this kind of fatty liver is prevented. It would appear that thyroxine not only antagonizes the effect of cortisone but also facilitates the mobilization of fat, which in turn is oxidized. Furthermore, thyroxine improves the utilization of carbohydrate in hypophysectomized or stalk-sectioned baboons receiving prolonged treatment with cortisone (unpublished data), thus revealing that the intolerance to carbohydrate induced by cortisone depends in some way on active fat synthesis and fat storage and on a different participation of insulin in metabolism. It may well be the case that thyroxine prevents the elaboration of Bornstein's metabolite which inhibits insulin or of Loubatières's alloxan-like substance which depresses the islets.

On the other hand, cortisone protects the hypophysectomized baboon from the grave constitutional reactions of thyroxine. It is tempting to ascribe this protective effect of cortisone to its role in fat metabolism, especially as it has been demonstrated that the feeding of fat can protect rats against the growth-inhibiting and lethal effects of excess thyroxine (Deuel, 1954).

The commanding role of thyroxine in preventing the cortisone fatty liver is demonstrated by the fact that the fatty livers of hypophysectomized or stalk-sectioned baboons treated for at least 90 days with cortisone will resolve almost completely within 21 days after the thrice-weekly injection of 0.5 mg. of thyroxine. We have reason for believing that thyroxine may be of some clinical value in treating the fatty livers which often appear in patients suffering from Cushing's disease or which develop in the course of chronic alcoholism.

In essence, then, the cortisone–thyroxine withdrawal fatty liver is no different from that produced after the prolonged administration of cortisone, except that in the former instance the liver is much more fatty and the speed of accumulation of fat in the liver is greatly accelerated. Both depend on the presence of excess cortisone, and both are associated with an intolerance to carbohydrate, suggesting a relative insufficiency of insulin. However, there can be little doubt that the sudden removal of thyroxine, as well as of cortisone, promotes a violent change in metabolism from one in which the oxidation of fat and carbohydrates is proceeding vigorously to one in which the utilization of carbohydrate is depressed. The conditions are thus created for the emergence of the intensely fatty liver which develops so characteristically in hypophysectomized and stalk-sectioned baboons.

Less easy to understand is the moderately fatty liver of hypophysectomized baboons receiving excess thyroxine. The grave constitutional reactions attended by the loss of appetite and consequent inanition could easily depress the pancreas. But, since the fatty liver also requires cortical hormone apparently in excess of that elaborated by the hypophysectomized baboon, it might be assumed that the thyroid stimulated adrenocortical activity. This explanation is unlikely, as we have demonstrated that thyroxine does not lead to a fatty liver in D.-H. insulin-deprived baboons. This kind of fatty liver still remains to be explained.

Relation of Liver Fat to Depot Fat

The remarkable lipaemia of depancreatized insulin-deprived baboons, and the expansion of the fat depots of cortisone-treated hypophysectomized baboons (Gillman

et al., 1957), more than suggests that the fat in the liver is closely linked to the factors which regulate the synthesis, oxidation, storage, and mobilization of depot fat. Barrett *et al.* (1938) and Stetten and Salcedo (1944) have demonstrated with the aid of deuterium that fat accumulating in the livers of rats treated with extracts of the anterior pituitary gland is mobilized from the depots. Tracer studies using ^{14}C have revealed that in insulin-deprived depancreatized baboons the fat is also probably mobilized into the liver from the depots (unpublished data).

Mobilization of fat into the liver, according to Levin and Farber (1951), involves two processes. First, the fat-mobilizing mechanism is sensitized by some fraction of the pituitary which apparently is neither growth hormone nor corticotrophin. Once this sensitization has been achieved the second process is initiated by the administration of corticotrophin or 11-oxycorticosteroids.

The experiments in D.-H. baboons disclose that in the absence of the pituitary the administration of cortisone will promote a fatty liver provided the insulin is inadequate or no insulin is supplied to the animal. If at the same time thyroxine is also administered the liver will accumulate massive amounts of fat. These experiments allow us to infer that a fatty liver can be produced in the absence of the pituitary gland in baboons, and that the dynamic relation, particularly between insulin and cortisone and also to a less extent between these two hormones and thyroxine, determines the presence or absence of fat in the liver and therefore also the storage and mobilization of fat from the depots. It would also appear that the preliminary sensitization process required by Levin and Farber before cortisone or corticotrophin can mobilize the fat may represent nothing more than depression of insulin secretion or a sudden change in one of the metabolic actions of insulin, where the insulin becomes insufficient to cope adequately with the oxidation of carbohydrates, thus creating an essential condition for the 11-oxycorticosteroids to mobilize the depot fat to the liver, an effect which then is potentiated by thyroxine.

The fatty liver following the administration of growth hormone is apparently also due to an absolute or relative insufficiency of insulin. Thus, Campbell *et al.* (1954) reasoned, "these observations on liver lipids lead again to the conclusion that growth hormone creates an increased metabolic demand for insulin which is countered in the intact animal by an increase in the rate of secretion of insulin by the islet cells." However, it is to be emphasized that a relative or absolute insufficiency of insulin alone will not produce a fatty liver unless there is also available a minimum amount of 11-oxycorticosteroids.

Rapid mobilization of fat from the depots alone need not lead to a fatty liver. We have indicated that the mobilization of depot fat by thyroxine in a stalk-sectioned or hypophysectomized baboon, rendered obese by prolonged cortisone treatment, is accompanied by a reduction in liver fat, despite the loss of weight. Amongst their other metabolic effects, therefore, insulin and cortisone stimulate fat synthesis and storage in the depots, while insulin and excess thyroxine promote fat mobilization and fat oxidation. Even if fat synthesis also occurs in the presence of thyroxine, as suggested by Wertheimer and Shapiro (1948), the net effect, so far as baboons are concerned, and having regard to the concentration of thyroxine used, is depletion of the fat depots and loss of body weight (Gillman and Gilbert, 1956b).

As reported previously, depletion of the fat depots after adrenalectomy of the baboon is not accompanied by the appearance of fat in the liver (Gillman and Gilbert, 1956c). Synthesis of fat and storage in the depots appears to require a minimal amount of cortical hormone as well as insulin, since if the latter is not available the fat is rapidly moved out of the depots into the liver. The synthesis, storage, mobilization, and oxidation of fat, therefore, are governed by a delicate interaction at least of insulin, cortical hormone, and thyroid hormone. The tendency towards fat synthesis following an increase of cortisone, for example, may be offset by a corresponding increase in thyroxine. The fat-mobilizing effect of insulin insufficiency may be counteracted by a depression in cortical hormone.

The promotion of the fatty liver by growth hormone, too, needs to be examined in terms of the dynamic relation existing between insulin, thyroxine and cortical hormone. In reviews of the literature, Young (1953) and Engel (1955) outlined the main effects of growth hormone on metabolism. These effects include the inhibition of the hexokinase reaction (Colowick *et al.*, 1947), stimulation of the conversion of amino-acids to protein, and inhibition of amino-acid catabolism (Russell and Cappiello, 1949; Russell, 1955), mobilization of fat from the depots to the liver (Szego and White, 1949; Greenbaum and McLean, 1953a), acceleration of fatty acid catabolism (Greenbaum and McLean, 1953b), and inhibition of oxidation of acetate via the Krebs cycle or the synthesis of fat from coenzyme A (Welt and Wilhelmi, 1950; Gurin and Brady, 1953). The metabolic processes regulated by growth hormone obviously couple protein synthesis to the metabolism of fats and carbohydrates. Within this metabolic framework, insulin, the cortical hormones, and thyroxine play a crucial part.

Insulin, for example, cannot participate equally intensively in facilitating the storage of glycogen, fat synthesis, fat storage, oxidation of carbohydrates, and protein synthesis without leading to a metabolic upheaval. Modulation of these several functions of insulin is achieved by the secretory activity of the other endocrine glands. In one endocrine setting, therefore, insulin may promote protein synthesis, while in another it may promote fat synthesis and storage, as we have seen in the case of the cortisone-treated hypophysectomized baboons. Acceleration of metabolism by excess thyroxine not only depletes the fat depots but also speeds up oxidation in the cortisone-treated hypophysectomized or stalk-sectioned baboons, and thus prevents the fatty liver. Both fat and carbohydrates are actively burnt.

Similarly, excess thyroxine arrests the growth of young baboons but induces weight loss in adult baboons (Gillman and Gilbert, 1956d). Then, too, the emphasis on protein synthesis resulting from the administration of growth hormone has repercussions on carbohydrate and on fat metabolism (Greenbaum, 1955; Engel, 1955), and therefore on the precise participation of insulin in metabolism as a whole. Greenbaum and McLean (1953a, 1953b) consider the accelerated fat mobilization as essential for the protein anabolic reaction to growth hormone. The central place of insulin in metabolism is therefore abundantly evident, especially as in the ultimate analysis the energy for all synthetic processes is derived from the oxidation of fats, carbohydrates, and proteins, and in these oxidative processes insulin is indispensable.

In viewing the role of any one hormone in fat metabolism as it affects particularly the development or the prevention of the fatty liver, the overall metabolic context, briefly indicated above, needs to be taken into account. However, it is equally clear that, whichever way a particular hormone alters metabolism, the fatty liver does not emerge in baboons unless insulin is relatively or absolutely insufficient and there is available an adequate amount of cortical hormone. If insulin is absolutely insufficient, as in depancreatized baboons, thyroxine certainly and probably also growth hormone will aggravate the fatty liver.

Fatty Liver of Endocrine Origin and Fatty Liver of Malnourished Human Infants

At the outset it may be stated that the exocrine part of the pancreas does not seem to regulate the fat content of the liver. In depancreatized baboons the amount of available insulin, rather than the pancreatic secretion, was the limiting factor in the production of the fatty liver. The atrophy of the pancreatic acini in malnourished infants may interfere with the absorption of food, and thus indirectly, via the endocrine glands, may affect the evolution of the fatty change.

No significant morphological difference can be found between the intensely fatty liver evoked in baboons by manipulating the endocrine glands and the spontaneously occurring fatty liver of the kind seen in acutely ill malnourished African infants. Indeed, during the progression and regression of the fatty change in baboons, the movement of fat into and out of the cells of the liver lobule follows a pattern similar to that we have observed in human infants. It therefore remains to ascertain whether there is any evidence in favour of the view here presented that the fatty liver of malnourished African infants is aetiologically similar to the kind described above in baboons.

As already mentioned in greater detail elsewhere (Gillman and Gillman, 1951), the fatty liver in African infants evolves rapidly and represents one of the manifestations of a partial metabolic disorganization occurring in an infant with a background of malnutrition. Malnutrition is required to produce a metabolic context in which a mild infection or some other minor stress at least will result in a relative or absolute deficiency of insulin in association with a relative or absolute hyperfunction of the adrenal cortex.

The insulin content of the pancreas of animals may be reduced either by a caloric insufficiency or by the substitution of a poor protein like gelatin for casein in an otherwise adequate diet (Best *et al.*, 1939; Haist *et al.*, 1940; Haist, 1944), or by a deficiency of methionine or cystine (Griffiths, 1950). A sudden loss of appetite, with refusal of food and consequent starvation, such as often happens in malnourished infants early during the acute episode, can reduce the insulin in the pancreas as occurs in animals (Haist, 1944).

The adrenal glands can also be modified by diet, as is clearly evident from the classical studies of McCarrison (1921) on pigeons, guinea-pigs, and monkeys. McCarrison drew attention to the greater sensitivity of the adrenal glands of younger than of older animals to the effects of malnutrition. He stated, moreover, that "the functional perfection of the adrenal gland is dependent on the quality of food." A deficiency of pantothenic acid (Ashburn, 1940; Melampy *et al.*, 1951; Winters *et al.*, 1952a, 1952b; Cowgill *et al.*, 1952), pyridoxine and aneurine (Antopol and Unna, 1942; Deane and Shaw, 1947), and vitamin C (Pfander and Mitchell, 1951) are all said to modify the structural integrity of the adrenal gland to a greater or lesser extent. Apparently, enlargement of the adrenal gland is more marked in partial than in complete inanition (McCarrison, 1921; Jackson, 1925). Hyperactivity of the adrenal cortex culminating in adrenal apoplexy, in association with hyalinization of the islets of Langerhans and dissociated pituitary function, has been described in baboons (Gillman and Gilbert, 1956e). Atrophy of the mucous membrane of the gastro-intestinal canal, the pancreas, and the salivary glands in fatal cases of kwashiorkor and infantile pellagra is reminiscent of similar phenomena in rats after hypophysectomy (Baker and Abrams, 1955). But the not-infrequent hyperactive adrenal cortex, as seen morphologically, recalls the dissociated activity of the pituitary gland described in malnourished baboons. There is more than suggestive evidence that both the islets and the adrenal cortex can be affected profoundly by diet.

During the acute episode in malnourished African infants the ensuing loss of appetite with consequent reduction in caloric intake can still further depress the insulin content of the pancreas, thus satisfying an essential condition for the production of the fatty liver. The slight intolerance to carbohydrate, detected after intravenously administered glucose (Niemeyer and Meneghello, 1950), the apparent inability of the liver to store glycogen (Holmes and Trowell, 1948), and the lipaemia in cases of kwashiorkor terminating fatally (Jayasekera *et al.*, 1951) are all consistent with an absolute or relative insufficiency of insulin. Then, too, the vacuolated nuclei observed in the livers of recovering infants (Gillman and Gillman, 1951) are reminiscent of those described in depancreatized baboons, and in hypophysectomized baboons chronically treated with cortisone. Such vacuolated nuclei are dependent on a measure of adrenocortical activity and on a relative or absolute insufficiency of insulin (unpublished data).

The information obtained from hypophysectomized or stalk-sectioned baboons developing a fatty liver after withdrawal of cortisone and thyroxine shows that neither the blood fats nor the resting blood sugar need be elevated, although an intolerance to carbohydrate can be demonstrated by the intravenous glucose-tolerance test. It is therefore unnecessary to presume a marked lipaemia or hyperglycaemia in all instances where there is a relative or absolute insufficiency of insulin.

As mentioned above, the atrophy of the lymphoid tissue and thymus, the oedema, and the intolerance of carbohydrate are suggestive of hyperactivity of the adrenal cortex. In terms of the experiments on baboons, even in the presence of normal adrenal function, a depression in insulin secretion would be sufficient to promote a fatty liver.

From the foregoing it is evident that the acutely developing fatty liver of malnourished infants may be immediately related causally to a disturbance of the dynamic relationship between insulin and the adrenocortical and thyroid hormones and not immediately to atrophy of the pancreatic acini. Although the disorder in fat metabolism is manifestly enacted in the liver, the cause for this fatty liver is apparently to be found not in the liver but in the endocrine glands. Finally, this investigation emphasizes the close relation between diet and the physiology of the endocrine glands, a relation which would well repay further investigation if other fatty livers having a seemingly different aetiology from that described in malnourished infants are to be understood.

Summary

Fatty liver has been produced consistently in the baboon by various endocrine techniques. Irrespective of the way a particular hormone altered metabolism, a fatty liver did not emerge unless insulin was relatively or absolutely insufficient and an adequate amount of adrenocortical hormone was available. It was demonstrated that in defined circumstances thyroxine could promote the resolution of a fatty liver.

Amongst their other metabolic effects, insulin and cortisone stimulated fat synthesis and storage in the depots, while insulin and excess thyroxine, even in the presence of excess cortisone, promoted fat mobilization and oxidation. A fatty liver was shown to be dependent at least on a dynamic relationship between insulin, the thyroid, and adrenocortical hormones.

It is suggested that the acutely developing fatty liver of malnourished African infants might be related to an acute endocrine disturbance involving the islets of Langerhans, the adrenal cortex, and the thyroid gland, and not necessarily to atrophy of the exocrine part of the pancreas.

We wish to thank Dr. E. Epstein for carrying out hypophysectomies and Mr. J. C. Allan, of the department of surgery, for performing the pancreatectomies on the baboons.

ADDENDUM.—Since this paper went to press we have been able to show that a saline suspension of acetone dried human anterior pituitary is capable of producing an intensely fatty liver, accompanied by severe constitutional reactions, within five days in a D.-H. baboon not receiving insulin. The contribution of somatotrophic hormone in conjunction with corticotrophin to the fatty liver of human infants still needs to be assessed within the endocrine context discussed above.

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For the past year a new residential school for spastics, "Scotscraig," has been open in Paisley. It is under the direction of the Scottish Council for the Care of Spastics. Once extensions have been completed, the school should have enough places to educate and treat suitable children from the West of Scotland. Cases are screened before acceptance by a panel consisting of an orthopaedic surgeon, a paediatrician, a child psychiatrist, and an educational psychologist. Apply for further details to the social worker, "Scotscraig," Park Road, Paisley.

BACTERIAL ENDOCARDITIS

SURVEY OF PATIENTS TREATED BETWEEN 1945 AND 1956

BY

A. ERIC DORMER, M.D., M.R.C.P.

Senior Medical Registrar, Medical Unit, St. Bartholomew's Hospital, London

Sulphonamides reduced the mortality of bacterial endocarditis from some 99% to 95% (Friedberg, 1950), but with the introduction of penicillin the cure of most patients at last became a possibility. The manner in which penicillin should be employed was elucidated in this country largely as a result of the Medical Research Council trials which were set up in 1945 (Christie, 1946, 1948, 1949; Cates and Christie, 1951). However, the Registrar-General (1955) showed that in 1949 the early mortality of bacterial endocarditis in the majority of teaching hospitals was 25% (of 124 cases), and for a smaller number of regional board hospitals the mortality was 31% (of 26 cases), while in 1951 these figures were still 19% (of 126 cases) and 40% (of 35 cases) respectively. The yearly mortality due to bacterial endocarditis in England and Wales (Registrar-General, 1955) showed a slight decline from 1938 which became steeper after 1944 when penicillin became available, but this improvement affected females to a greater extent than males. Since 1952 the mortality among males has remained more or less constant, while for females there has been a further slight decrease (Fig. 1).

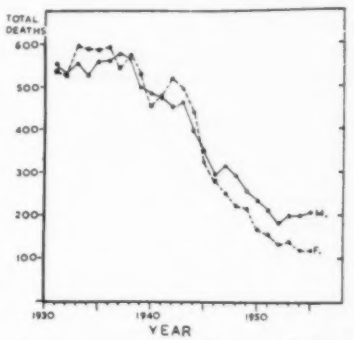

FIG. 1.—Yearly total deaths in England and Wales due to bacterial endocarditis.

Because of the persistence of bacterial endocarditis as a cause of mortality, it was decided to survey all the patients who had been treated in this hospital for the disease during the period that antibiotics had been freely available. This survey therefore covers the years 1945 to the end of 1956, and concerns a total of 82 patients (58 male and 24 female); their heart lesions are shown in Table I. In a few cases initial investigation or treatment had been started elsewhere. All patients were traced and survivors followed until 1956 or 1957 with the single exception of one female who went abroad in 1954, four months after cure. Among these 82 patients there were, because of second attacks, a total of 97 separate infections, 22 of which

TABLE I.—*Heart Lesions—All Patients*

Rheumatic heart disease		63
Significant aortic disease	37	
Simple mitral stenosis	7	
Congenital heart disease		13
Ventricular septal defect	7	
V.S.D. and pulmonary stenosis	1	
Persistent ductus arteriosus	1	
Aortic stenosis	3	
Multiple defects	1	
Spirochaetal aortic disease		2
Arteriosclerotic heart disease		4

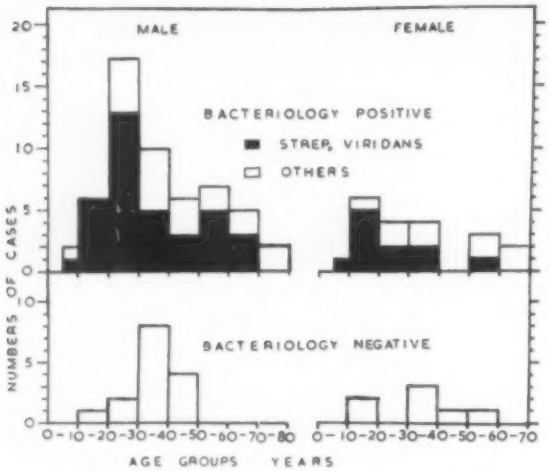

FIG. 2.—Present series. Age groups and bacteriology.

(15 male and 7 female) were bacteriologically negative. The age distribution of the patients with these infections is shown in Fig. 2.

Results of Treatment

Of the 14 patients who had survived treatment in 1945 one died after reinfection with a different and resistant organism, a further two (both having severe rheumatic heart disease) died as a result of heart failure three years after cure, while 11 patients were alive 11 years later.

Since 1946 51 bacteriologically positive patients have been treated, but 15 (29%) failed to survive treatment (Table II), while a further 13 have died (Table III), seven of them within two years of treatment and from causes attributable to the results of their infection, making a total early and late mortality, therefore, of 43%. For the remaining patients of this group the present duration of survival is shown by Table IV.

TABLE II.—*Bacteriologically Positive Patients Dying Before Discharge*

Year	Sex	Age	Total Length of Illness (Months)	Organism	Remarks
				Undiagnosed in Life	
1948	F	54	?	—	S.B.E. incidental to other disease
1956	M	73	?	—	S.B.E. incidental to other disease
1956	M	72	4	—	Cerebral embolus
				Resistant infections uncontrolled at death	
1955	F	52	1	Coag. pos. staph.	—
1953	M	40	3	*Staph. albus*	—
1953	M	52	2	Corynebact. diphtheroid	—
1947	M	63	20	*Str. viridans* (resist.)	—
1951	M	63	6	*Str. faecalis*	—
1955	F	19	20	.. ..	—
				Uncontrolled at death	
1955	M	36	2	Micro-aerophil. strep.	Coronary embolus—2nd week of treatment
1950	M	8	5	.. ..	Poor response to treatment
1956	M	58	5	*Str. viridans*	After 1 month's treatment—cerebral embolus
				Controlled at death	
1954	M	22	7	*Strep. viridans*	Heart failure 1 month after completing treatment
1954	M	23	7	.. ..	Heart failure 6 weeks after completing treatment
1950	F	36	?	*Str. faecalis*	Heart failure 2 weeks after completing treatment

TABLE III.—*Bacteriologically Positive. Deaths After Cure*

Sex	Age at Death	Infection: Organism	Infection: Year	Length of History before Curative Treatment (Mths.)	Remarks	Death: Time from Cure (Mths)	Death: Cause
M	61	*Str. viridans*	1955	6	Heart failure before treatment	1	Heart failure, Uraemia
M	51	.. ..	1954	5	Valve rupture 1 month from cure	3	Heart failure
F	55	.. ..	1948	1	Heart failure during treatment. Syphilitic heart disease	3	.. ..
M	49	*Bact. fusiformis*	1953	3	Heart failure during treatment	4	.. ..
M	62	*Str. viridans*	1954	2	.. ..	4	.. ..
M	24	*Str. viridans* (resist.)	1951	11	.. ..	6	.. ..
M	26	*Str. viridans*	1946	3	—	24	Rupture old cerebral mycotic aneurysm
F	69	Non-haem.o-lytic strep.	1953	1	Heart failure 4 months after cure. Syphilitic heart disease	31	Heart failure
M	37	*Str. viridans* (resist.)	1946	5	Fibrillation 4 years after cure	60	.. ..
M	32	*Str. viridans*	1948	1	Sudden death	49	? Cerebral embolus
M	49	.. ..	1950	1	Second attack	72	2nd cerebral embolus

Two other deaths were unrelated to heart lesion.

TABLE IV.—*Bacteriologically Positive Patients Surviving*

	Year from Cure of First Attack										
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
No. of patients ..	2	5	1	0	1	2	3	3	2	1	3

Delay in Diagnosis

The delay in diagnosis from the time of onset of symptoms has been assessed where possible and is shown in Fig. 3; this indicates also the number of patients who either knew that they had congenital heart disease, had had previous bacterial endocarditis, or who would have suggested the possibility of an abnormal heart by giving a history of rheumatic fever. That delay could be considerable is emphasized by the number of patients who had been infected for over three months before being correctly diagnosed. Since a high index of suspicion for bacterial endocarditis must be entertained in any patient having an abnormal heart, the large proportion of patients in this series who would on history-taking have indicated such an abnormality is of interest.

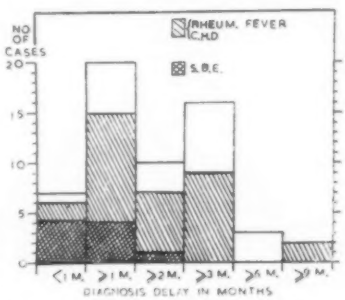

FIG. 3.—Present series. Delay in diagnosis.

It was obvious that, when less typical features of endocarditis predominated, delay in diagnosis tended to be considerable, for such features may blind the clinician to the other signs and symptoms which a fuller history and examination would reveal.

The presence of pains in joints often appeared to confuse, and in eight patients joint pains, sometimes in a single joint, were a predominant complaint. In a further two patients effusions into a knee-joint were found on initial examination. Sometimes there may be confusion with rheumatic fever, and indeed two patients were so misdiagnosed initially,

while in a third, on good grounds, both diseases were assumed to be present.

Bacterial endocarditis may start with or follow immediately upon an infection of the upper respiratory tract, and in the series diagnosis was delayed in five patients who were diagnosed originally as having influenza, failure to recover from this being attributed to post-influenzal depression.

Old age (4 patients), the presence of other conditions (3), gross purpura (2), and short courses of antibiotics for unexplained fever (8) were further causes of delay.

In most cases murmurs were obvious, and little doubt could be entertained concerning the abnormality of the heart, but in each of three patients the only abnormality present was a short apical systolic murmur whose significance could easily have been overlooked.

Certain other aspects, while not greatly delaying diagnosis, gave cause for comment. Retinal haemorrhages were a common feature, but in four patients papilloedema, whose occurrence in cases of bacterial endocarditis was well reviewed by Falconer (1910), was also present. In one of these patients the association of papilloedema and mental change caused serious consideration as to whether an intracranial tumour might also be present, but the mental changes improved with treatment of the endocarditis and no intracranial abnormality was subsequently shown at post-mortem examination. Apart from cases with cerebral embolus, mental confusion was a marked feature with two patients, both of whom were in the later age groups, in which mental impairment often accompanies infection.

Investigations such as the erythrocyte sedimentation rate can usually be relied upon to give some indication of infective processes, and in only two patients of the present series was the initial recording (Westergren) less than 10 mm. in one hour, while no values were below 5 mm. The haemoglobin level sometimes drew attention to the disease, but its degree of departure from normal tended to be related to the length of history, so that it becomes of less value if the accent is to be on early diagnosis. The total white blood count was of no diagnostic value: of 51 cases, it was less than 5,000 in 3, between 5,000 and 10,000 in 25, between 10,000 and 15,000 in 16, and between 15,000 and 20,000 in 7.

Only four patients who were bacteriologically positive had established auricular fibrillation when the disease set in, and two of these were examples of post-operative staphylococcal endocarditis; a further three patients had fibrillation during treatment. By contrast auricular fibrillation was established in 5 out of 22 bacteriologically negative patients at the onset of their disease.

Precipitating Factors

Eleven patients gave a history which strongly suggested that extraction of infected teeth without antibiotic cover was the precipitating factor; nine of them were infected with a *Streptococcus viridans*, while two had a micro-aerophilic streptococcus. Questioning for a history of rheumatic fever or of known heart disease would have obtained a positive answer in seven of these patients.

Records concerning dental extractions performed under antibiotic cover are not complete, but at least 43 patients who have previously had bacterial endocarditis had teeth extracted, on 57 occasions, under antibiotic cover without subsequent incident. Two patients, however—one with and one without a previous history of bacterial endocarditis—were infected following dental extractions under penicillin cover. One of these became infected with a highly resistant organism and has been reported already (Cates, Christie, and Garrod, 1951). The second patient, who had congenital aortic stenosis, was investigated by cardiac catheterization and cardioangiography on August 29, 1951; procaine penicillin, 300,000 units, was given twice daily on the 29th and 30th and the wound healed well. On September 5 eight teeth were extracted, crystalline penicillin, 500,000 units, being given one hour before extraction, followed by procaine penicillin, 300,000 units twice daily, starting at about the time of extraction and carried on for three days. Symptoms started soon afterwards, and subsequently blood culture yielded a *Str. viridans* having approximately four times the resistance to penicillin of the Oxford staphylococcus.

Ten patients were found to be edentulous, although in none of these was the absence of buried roots confirmed by radiology. Table V shows the relevant details of these cases. The patient infected with a micro-aerophilic streptococcus had had a dental clearance four months earlier, and this appeared to be the precipitating factor. Only one edentulous patient was infected with *Str. viridans*, and this was proved to be highly resistant. He was found on admission to have an infected ulcer in the mouth due to the abrasive effect of ill-fitting dentures, and it was thought possible that his infection had resulted from this.

TABLE V.—*Patients Edentulous on Admission*

Sex	Age	Organism
M	56	*Str. faecalis*
M	49	*Bact. fusiformis*
M	72	Undiagnosed in life
M	73	" "
M	45	Negative
M	46	"
F	50	"
F	52	"
M	67	Micro-aerophilic streptococcus
M	62	*Str. viridans*

One case was of interest in that it demonstrated the manner in which a focus of infection may persist at the site of dental abnormality. A 24-year-old man had had two teeth extracted in November, 1946, but there was then a gap of seven months before the onset of bacterial endocarditis. He was admitted to hospital on March 26, 1948, having been treated at home with penicillin (the type of preparation being unknown), 500,000 units twice daily, from March 19 to 26. Blood culture taken on April 16 was the first to yield a positive result, growing a micro-aerophilic, slightly α-haemolytic, streptococcus having half the resistance to penicillin of the Oxford staphylococcus as judged by bacteriostatic tests. Treatment, begun on April 26, consisted of crystalline penicillin, 62,500 units by intramuscular injection every three hours, the penicillin titre of the serum just before the next injection was due being 0.09 u./ml. After an initial response further spikes of fever were recorded, but another blood culture on June 1 was sterile. Full dental examination on admission had shown healthy gums and teeth apart from one tooth which on *x*-ray examination showed apical rarefaction. Extraction of this tooth on June 11 revealed a granuloma attached to one of the roots. Culture from the surface of this yielded a very scanty growth of indifferent organisms, but an aerobic culture from the interior of the granuloma yielded a profuse growth of a streptococcus which was considered to be the same organism as had been obtained from the blood. Subsequent recovery was uninterrupted.

Of those cases infected with a *Str. viridans* (totalling 47) and with no history of recent dental manipulations, two

TABLE VI.—*Precipitating Factors—Non-dental*

Year	Age	Sex	Organism	Source of Infection
1950	62	M	*Str. faecalis*	Prostatectomy
1950	36	F	" "	Therapeutic abortion
1954	19	F	" "	" "
1952	25	F	" "	Abortion
1955	70	F	" "	Operation for urethral caruncle
1956	34	M	Micro-aerophilic strep.	Aural sepsis
1948	48	M	Coag.-neg. staph.	Septic spot scratched by comb
1955	52	F	Coag.-pos staph.	Infected eczema
1956	21	F	" "	Boil
1953	40	M	Coag.-neg. staph.	Mitral valvotomy
1955	40	F	Coag.-pos. staph.	" "
1954	31	M	Negative	Cardiac catheter

patients on full dental examination, which included *x*-ray films of the teeth, had no evidence of disease of teeth or gums.

Apart from 11 cases attributable to dental sepsis the precipitating factor could be identified in 12 patients; the details are shown in Table VI.

TABLE VII.—*Results of Blood Culture*

Organism	No. of Infections	No. of Cultures to Obtain Positive			Organism	No. of Infections
		1	2	More than 2		
Str. viridans:						
Insufficient information	8				Staphylococcus (coag.-neg.)	3
Sensitive to 0·04 u. or less penicillin ml.	27*	25	1	1	Staphylococcus (coag.-pos.)	3
Sensitive to 0·04–0·2 u. penicillin ml.	6	6			Corynebacterium diphtheroid	1
Sensitive to >0·2 u. penicillin ml.	6	6			*Bact. fusiformis*	1
Micro-aerophilic streptococcus	8†	6	1	1	Undiagnosed before death	3
Other haemolytic streptococci	2				Bacteriologically negative	22
Non-haemolytic streptococcus	1	1				
Str. faecalis	6					

* Six with fewer than 10 colonies per ml.
† Two very resistant; 6 sensitive to <0·09 u. penicillin per ml.

Organisms

Table VII shows the details of recovery of organisms, the proportions of the types commonly found being very similar to those reported in the literature. In two cases in which blood culture yielded scanty growth of organisms and there was doubt about whether they were in fact contaminants, agglutination tests with the patients' serum enabled the question to be settled. Although growth sometimes did not appear before the seventh day, most organisms, particularly the *Str. viridans*, were recovered with the first blood culture.

Morbidity

Some of the complications found are discussed below and shown in Tables VIII to X; the more serious of these considerably influenced the mortality of the disease.

Mycotic aneurysms occurred in eight patients, being commoner in young males (Table VIII). The 67-year-old

TABLE VIII.—*Arterial Mycotic Aneurysms*

Age	Sex	Organism	Site	Remarks
21	M	*Str. viridans* ..	Brachial	Excised during treatment
40	F	Staph. (coag.-pos.)	Popliteal	.. .. ..
24	M	Micro-aeroph. strep.	Int. iliac. Inf. gluteal	Tied .. ..
26	M	*Str. viridans* ..	Radial	Excised 3 months after treatment
67	M	Micro-aeroph. strep.	Popliteal	Tied soon after treatment
23	M	*Str. viridans* ..	Int. carotid	Int. carotid tied 1 month after treatment.
			Hepatic	Found at necropsy
26	M	.. .. ..	Cerebral	Burst 2 years after bacteriological cure
52	M	*Corynebacterium* ..	Popliteal	Present at death—infection uncontrolled

man had elsewhere been treated with corticotrophin when a biopsy of a lump had mistakenly been thought to indicate a diagnosis of polyarteritis nodosa. Lambert Rogers (1956) also noted a preponderance of young males when he reviewed the association of mycotic aneurysm and bacterial endocarditis.

Major embolic phenomena occurred on 39 occasions, as shown in Table IX, renal and splenic emboli being excluded because of the uncertainty of records. Laparotomy was performed on one patient who presented with superior mesenteric embolus and he survived, but the other cases of this condition were diagnosed clinically and treated conservatively, and all but one survived.

Six patients had considerable renal involvement early in the disease, with proteinuria and many casts; three of them

TABLE IX.—*Major Embolic Phenomena*

Artery	No. of Patients	Remarks
Cerebral	5	Severe, with little or no recovery (early death in 2)
	6	Mild, with considerable recovery
Coronary	3	All early death
Mesenteric	5	Laparotomy in one
Pulmonary	10	4 patients with V.S.D. had 7 major infarcts. Pleural effusion in 3 patients
Retinal	1	
Upper limb: proximal ..	1	
Upper limb: distal ..	5	
Lower limb: distal	3	
Spleen and kidney		Not presented

TABLE X.—*Valve Rupture*

Sex	Age	Organism	Length of History before Treatment (Months)	Site	Time of Rupture in Relation to Treatment (Weeks)	Length of Survival after Rupture (Weeks)
		Proved at Necropsy				
M	22	*Str. viridans*	11	Aortic	During	4
M	51	.. ..	5	Mitral	3 after	6
M	23	.. ..	4	Aortic	20 after	1
M	24	.. ..	10	..	During	16
M	52	Corynebacterium diphtheroid	Few	Sinus of Valsalva to right auricle	..	Nil
		Diagnosed clinically—unproved at necropsy				
M	49	*Bact. fusiformis*	3	? Mitral	During	24

survived, one continuing with a slight degree of proteinuria; in those who did not survive, renal failure contributed significantly to death. Progressive renal disease is a complication which can follow cure of endocarditis, but in this series no cases of late renal failure have so far been encountered.

Damage at the site of injection, which was commoner with the early forms of penicillin injections, has been unusual of recent years, but a sterile abscess was seen in two patients, each of whom, infected with a resistant organism, was being treated with streptomycin and with large doses of penicillin. The possibility of tissue reaction is, however, important in so far as it may contribute to persistence of fever and a raised erythrocyte sedimentation rate.

It was often the case with patients treated in 1945 that their fever did not abate until treatment stopped, and the problem has arisen in two cases of recent date. In one of these the persistence of some fever led to the abandonment of the correct form of treatment, which was not resumed until some months later, while in the other the dosage of antibiotics was probably pushed unnecessarily high. In case of doubt the bacteriologist can help in deciding whether there is an adequate bactericidal level of antibiotics in the serum.

Urticaria occurred in five patients treated with penicillin and was associated in one with alarming collapse and a rigor soon after her first injection. In three patients these reactions were severe enough to hold up treatment, but in each case desensitization was effected rapidly by the simultaneous use of penicillin and an antihistamine, as has been described by Maslansky and Sanger (1952), Balme and Dormer (1954), and Robinson and Binns (1954).

After streptomycin treatment three patients had no vestibular function remaining, while in a fourth there was considerable impairment of function. When penicillin is used in combination with streptomycin the dose of 4 g. a day of the latter, as recorded by Cates *et al.* (1951) and still quoted (Brewis, 1956), is probably excessive, 2 g. a day being now usually employed, although in particular circumstances and with the guidance of the bacteriologist this may require modification. There is evidence that streptomycin given as a mixture of streptomycin sulphate and dihydrostreptomycin results in less damage to the eighth nerve, but the more severe disabling effects of dihydrostreptomycin on the auditory component must be borne in mind.

Recurrence

Relapse of infection in some patients at the start of this series occurred early, and it is apparent that the dosage of antibiotics had been inadequate. All were finally cured by more intensive treatment. In a patient treated more recently the infection relapsed early when it was assumed to have been eradicated; the case report is here presented.

A girl, who had a history of two attacks of rheumatic fever and whose heart showed signs of mitral stenosis and aortic incompetence, had teeth extracted without antibiotic cover in 1951 at the age of 17. Within two months the full clinical picture of bacterial endocarditis developed, but diagnosis was delayed a further four months. Two blood cultures then proved to be negative, but she responded completely to a six-weeks course of crystalline penicillin, 500,000 units every three hours. Two years later, in October, 1953, teeth were extracted under cover of penicillin, and one month later a therapeutic abortion was carried out without antibiotic cover. Again she had symptoms of bacterial endocarditis, and in December a *Str. faecalis* was recovered from the blood. From then on, until she was referred for treatment nine months later, she received six different antibiotics, alone or in combination according to 11 dosage schedules, with little more than temporary control of the disease. In September, 1954, the *Str. faecalis* was again recovered and put up against penicillin, streptomycin, oxytetracycline, chloramphenicol, erythromycin, and bacitracin, alone and in pairs, but only penicillin (10 u./ml.) and streptomycin (10 µg./ml.) combined exerted a bactericidal effect and sterilized the medium. She was treated with crystalline penicillin, 2.5 mega units three-hourly for six weeks, together with streptomycin, 1 g. twice daily for the first week, followed by 0.5 g. twice daily, and this dosage gave adequate blood concentration. She rapidly became afebrile and remained so for six weeks after completion of the drug course before being discharged from hospital, but two weeks after that the signs and symptoms of infection recurred and *Str. faecalis* was again found. Unfortunately she was not referred back for treatment. Further palliative courses of bacteriostatics were given elsewhere and she died in August, 1955, necropsy revealing unhealed vegetations on both mitral and aortic valves extending widely on to the wall of the left atrium and left ventricle.

The relapse after the major course of combined penicillin and streptomycin was surprising, although it was realized that the dosage of streptomycin was being kept to a minimum to prevent extension of the already severe vestibular damage. Probably a longer course should have been given in view of the very long history and presumably large vegetations.

TABLE XI

Sex	Age	First Infection		Second Infection		Time Interval		Remarks
		Year	Organism	Year	Organism	Yrs.	Mths.	
M	21	1945	*Str. viridans*	1949	Haem. strep.	4	1	
F	22	1945	.. ..	1954	Negative	9	0	Clinically certain
M	45	1945	.. ..	1948	Coag.-neg. staph.	2	3	
M	25	1945	.. ..	1945	*Str. viridans*	0	10	Possibly same organism
M	16	1945	.. ..	1955	Haem. strep.	9	8	
M	19	1945	.. ..	1950	Coag.-neg. staph.	4	10	
M	38	1945	.. ..	1956	Micro-aero. strep.	11	9	
M	57	1945	.. ..	1950	*Str. faecalis*	5	0	Died
M	37	1946	.. ..	1950	*Str. viridans*	4	8	Second followed dental ext.; diff. sensitivity
M	20	1947	.. ..	1952	Negative	4	9	Some doubt
M	26	1947	.. ..	1949	..	2	10	Clinically certain
M	24	1948	Micro-aero. strep.	1956	..	8	2	.. ..
F	11	1949	*Str. viridans*	1952	*Str. viridans*	2	11	Organisms had similar sensitivity
M	19	1950	.. ..	1953	.. ..	2	6	
F	16	1952	Negative	1953	*Str. faecalis*	1	10	Died

In all, 15 of the 82 patients who form this series were diagnosed as having two attacks of endocarditis, the details being presented in Table XI. In 11 the underlying heart disease was rheumatic, while in 4 a ventricular septal defect was present.

Treatment

For penicillin-sensitive organisms there was experiment originally with the daily dosage of penicillin, but with the publication of the M.R.C. report in 1948 crystalline penicillin given by intramuscular injection at three-hourly intervals to a total of 2 mega units daily and for six weeks became the practice throughout the hospital. Even on this regime one patient with a sensitive *Str. viridans* infection failed to respond until the daily dosage was raised to 4.8 mega units.

The practice of treating sensitive infections with intramuscular crystalline penicillin continued through to 1957, but since about 1953 physicians have tended to use larger doses at greater intervals, the commonest regime being that of 1 mega unit every six hours. This, while adequate for most patients, proved to give inadequate control in one where the organism (a *Str. viridans*) had 1.4 times the resistance of the standard staphylococcus, and in a further patient infected with a non-haemolytic streptococus sensitive to 0.2 unit of penicillin per ml., 3 mega units every six hours proved sufficient after 2 mega units every six hours had been inadequate.

For the resistant organisms in this series penicillin and streptomycin proved to be the most useful combination of drugs. For all the strains of *Str. faecalis* such a combination proved bactericidal, while in one strain a lesser effect was obtained with streptomycin and erythromycin and with streptomycin and oxytetracyline. Such action was not found with any other individual drug or pair of drugs from among those tested, which included penicillin, streptomycin, oxytetracycline, chloramphenicol, erythromycin, and bacitracin.

The combination of streptomycin with penicillin also effected cure in two recent staphylococcal infections. In one of these penicillin alone, while effecting stasis, did not sterilize the medium. Before referral this patient had received four antibiotics in six different combinations and schedules of dosage over a period of seven days. The other staphylococcus proved to be a slow penicillinase producer but was eliminated by crystalline penicillin, 7 mega units, together with streptomycin, 0.75 g., every eight hours over five weeks.

Bacteriologically Negative Group

This group, consisting of a total of 22 patients, five of whom at some stage had a bacteriologically positive infection, is not easy to classify but may be subdivided as follows.

Group 1.—This group consists of 16 patients who had the clinical features of bacterial endocarditis and for whom, despite negative blood cultures, there seemed no reason to doubt the diagnosis. Ventricular septal defect was present in three. Twelve patients showed response to penicillin in ordinary doses, although four died of early complications (three of heart failure and one following a cerebrovascular acident). In four patients penicillin was not sufficient or was not used alone to control the disease. One patient relapsed immediately on cessation of massive penicillin dosage and died of heart failure during chloramphenicol treatment, post-mortem examination revealing healing endocarditis of the aortic valve. One patient with congenital aortic stenosis failed to respond to penicillin in a daily dose of 2 mega units but apparently responded to a six-weeks course of penicillin, 10 mega units, combined with streptomycin, 2 g. a day, only to relapse. This combined course was repeated and controlled the disease. The other two patients were cured by a single course of penicillin and streptomycin in combination.

Group 2.—This group consists of those patients presenting with heart disease and with fever, atypical features being encountered. All six patients were in gross heart failure, five of them having auricular fibrillation. Haemoptysis was a feature in all, and the problem is posed

whether the fever is attributable to inflammation associated with areas of pulmonary infarction. One patient tentatively diagnosed as having bacterial endocarditis together with gross heart failure from tight mitral stenosis had fever which failed to respond to antibiotics and failure was intractable; post-mortem examination showed no evidence of bacterial endocarditis. Where doubt exists it is obvious, however, that antibiotics must be given.

Discussion

Any attempt to reduce the incidence of bacterial endocarditis involves the recognition of those with heart disease, and the awareness and control of processes leading to bacteriaemia in such patients. The high proportion of patients in the present series who were aware that they had an abnormal heart or who would have given a history of rheumatic fever is of interest and shows the value of simple questioning.

Examination usually reveals obvious valvular abnormality, but the occurrence of endocarditis in the absence of a heart murmur has been emphasized by MacGregor (1956). The so-called innocent apical systolic murmur can be particularly difficult, and may be associated with bacterial endocarditis as recorded in the present series. One of these patients, before the onset of his bacterial endocarditis, had been confidently diagnosed as having such a murmur, and a phonocardiographic recording of it had appeared in a textbook as an illustration of an innocent murmur.

The risk of infection following surgery is a hazard for those with abnormal heart valves, and many cases are recorded—for example, following cardiac catheterization (Winchell, 1953), after cardiac surgery (Fleming and Seal, 1955; Andreassen and Jensen, 1956), while Merritt (1951) recorded an incidence of eight cases of endocarditis, seven of them due to *Str. faecalis* following 7,000 transurethral prostatic resections, seven of them occurring among the 70 patients with known heart disease. In the present series there are 12 examples of infection from such sources, but it is probable that sepsis associated with teeth is a much more frequent source.

The infrequency of *Str. viridans* endocarditis in the edentulous has been emphasized (Hobson and Juel-Jensen, 1956), and this is borne out by the present series. But to argue thereby that patients who have once had bacterial endocarditis should be rendered edentulous is a programme of despair which might logically be extended to include all patients with congenital or acquired valvular heart disease. Davies (1957) recorded a well-documented case of a *Str. viridans* infection in an edentulous patient. In addition, if the ulcer resulting from ill-fitting dentures be accepted as the cause of the *Str. viridans* infection in one of the cases here recorded, then even wholesale extraction will not suffice. Rather it is advocated that a much higher standard of observation and of dental care should be instituted. The necessary standard means that dentists should ask simple questions regarding heart disease and rheumatic fever before extracting teeth in their patients; that all patients known to be at risk should have regular and close dental care; that adequate examination of patients not often seen involves x-ray examination of the teeth; that all extractions in susceptible patients should be performed under antibiotic cover started only just in time to afford adequate blood levels by the time of extraction; that following such extractions, and because antibiotic cover does not always prevent infection, patients should specifically be warned to report early should untoward symptoms arise.

Early diagnosis is obviously of the greatest importance, so that the possibility of bacterial endocarditis must be borne in mind when unusual symptoms in those patients with abnormal hearts are being considered. The possibility of complications of the disease which contribute significantly to its morbidity and mortality constitutes a spur to early diagnosis, for in the present series only 50% of the patients escaped without some more or less unpleasant complication. Wedgwood (1955) has emphasized the delay that often occurs, and in the series here recorded the high proportion of patients infected for at least three months before diagnosis has already been mentioned, atypical features at the onset of the disease being regarded as contributing largely to such delay.

The recognition of bacterial endocarditis in the elderly is often not considered and may be particularly difficult (Anderson and Staffurth, 1955), for as a rule other conditions are present and cerebral symptoms such as confusion appear more easily. Fig. 4, constructed from the Registrar-

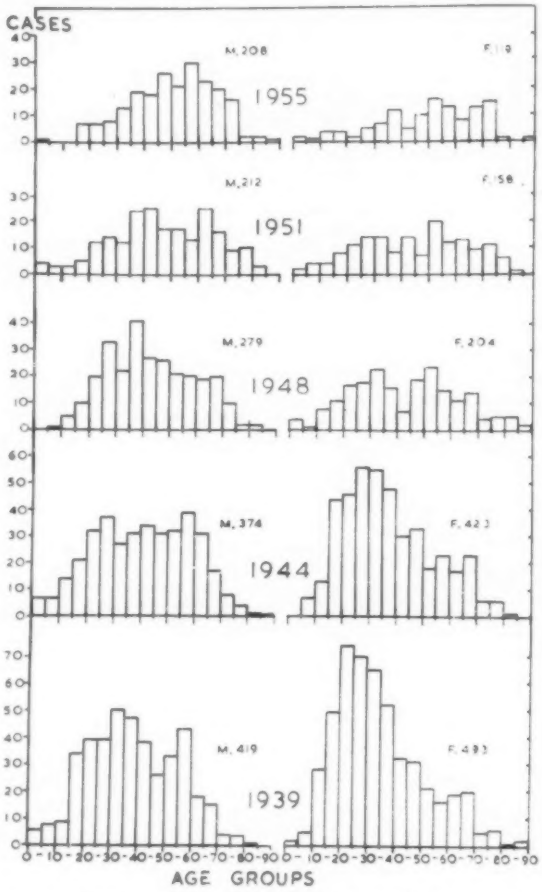

FIG. 4.—Deaths in England and Wales due to bacterial endocarditis: variation with age groups.

General's *Statistical Review for England and Wales*, illustrates the change in the age distribution of mortality which has occurred since bacterial endocarditis became a curable disease and emphasizes that amongst the higher age groups the greater proportion of fatal cases are now to be found. Because of age trends of the population and the greater ability to control the effects of heart disease, the appearance of bacterial endocarditis in the elderly is likely to remain important.

The treatment of bacterial endocarditis has been reviewed by Beeson (1955), and the *British Medical Journal* (1955) states that, since the M.R.C. trial, change in the form of treatment has been a matter of individual experiment.

In the present series change from three-hourly to six-hourly injections of penicillin has been fully justified, for the large doses at less frequent intervals maintained adequate blood levels equally well. But reduction of the length of treatment is on less certain grounds; for, while it may be adequate for some, unnecessary exposure to risk of relapse for a proportion is unjustifiable. Some of the present series

of patients died from complications of endocarditis at about the time of completion of a six-weeks course of antibiotics adjudged to be curative, and, although no detailed study was made at necropsy concerning the viability of the bacterial colonies seen, their appearance gave no grounds for hope that, in these cases, several weeks less of treatment would have sufficed. In addition a case has already been quoted in which even six weeks was not long enough to effect cure.

For penicillin-sensitive organisms fever that continues despite treatment may be due to systemic reaction to the antibiotic or to inadequate dosage. When considering this latter aspect it must be remembered that, while for streptococci of oral origin the bactericidal and bacteriostatic levels of penicillin are usually very similar, they are not always so, and this may explain failure of otherwise apparently adequate therapy (Berntsen, 1955).

Cure of infection with so-called resistant organisms by the use of bacteriostatic drugs is not to be expected, and a drug or combination of drugs having bactericidal action must be sought (Garrod, 1953). The most generally useful combination at present is penicillin (10 to 20 mega units a day) with streptomycin 2 g. daily. But it is emphasized that treatment of such cases is part of a campaign planned in full co-operation with the bacteriologist, and rapid switching of drugs and dosage schedules merely serves to confuse the issue and may kill the patient. Should sensitivity reactions to the chosen bactericidal drug occur the lethal nature of bacterial endocarditis requires that rapid desensitization should be attempted in preference to reversion to treatment using bacteriostatic antibiotics.

Summary

The results of treatment of bacterial endocarditis from 1945 to 1956 are presented. The immediate mortality has been about 25%. Delay in diagnosis is still considerable, and is discussed. The part played by teeth in the disease is emphasized. So far, there has been a late recurrence rate of some 18%. The disease has its greatest mortality, and is more often missed, among the older age groups.

I am grateful to the medical, surgical, and dental staffs of St. Bartholomew's Hospital for allowing me to follow and report in summary cases treated by them, and to the department of bacteriology, by whose considerable efforts treatment has been guided. This study was started with the encouragement of Professor R. V. Christie and of Dr. G. W. Hayward, who has been kind enough to offer advice, and was continued on the medical unit under Dr. E. F. Scowen. I also wish to express my thanks to Dr. J. E. Cates, who followed cases treated in the first half of the period under review and who facilitated my own work by allowing me access to his records.

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FURTHER STUDIES ON THE TRANSMISSION OF STAPH. AUREUS

BY

RONALD HARE, M.D.
Professor of Bacteriology and Honorary Consulting Bacteriologist to St. Thomas's Hospital

AND

MARK RIDLEY, M.B., B.Chir.
Lecturer in Bacteriology
From the Department of Bacteriology, St. Thomas's Hospital Medical School, London

It is now generally assumed that, except for pyogenic infections, the principal reservoir of *Staph. aureus* is the anterior nares of normal humans beings, and that there is a constant passage of this organism from person to person to produce the carrier condition or, when susceptible tissues are available, clinical infection.

The work of Duguid and Wallace (1948) and Hare and Thomas (1956) would suggest that direct transmission from carrier to recipient seldom takes place by means of droplets or droplet nuclei expelled from the nose. An indirect route is more probable, the first step being contamination of the skin and clothing of the carrier. Thence the organisms may reach a recipient who touches the carrier, by carriage on objects such as bedding or towels which have been in close physical contact with the carrier, or by air-borne particles released from his skin or clothing by friction, movement, or washing.

If transmission of *Staph. aureus* occurs in this way the numbers and distribution of the organism on the skin and clothing may govern the ability of the carrier to transmit his organisms to others. Investigation of this forms the first part of our paper. The second part gives details of experiments in which the ability of carriers to transmit their organisms by air-borne particles was assessed.

Experimental Methods

Media.—Isolation of *Staph. aureus* from the nasal cavity, skin, clothing, and air was invariably carried out on nutrient-agar plates containing phenolphthalein diphosphate. Made up in a concentration of 0.5%, it was sterilized by filtration and sufficient added to the melted agar immediately before the plates were poured to give a final concentration of 0.01% (Barber and Kuper, 1951; Hare and Thomas, 1956).

Isolation of Staph. aureus.—After incubation for 24 hours on the above medium, the plates were held face downwards over the neck of a bottle of strong ammonia; colonies of *Staph. aureus* turn red, thus enabling counts to be made of the number present. But, since other organisms may produce a similar coloration, representative colonies were invariably purified by plating and identified as *Staph. aureus* only if they were coagulase-positive and microscopically typical.

Contamination of Skin.—This was estimated by rubbing large cotton-wool swabs moistened with broth over an area of approximately 16 sq. cm. at each site. The swabs were immediately rubbed over the whole surface of phenolphthalein diphosphate nutrient-agar plates. With some carriers the whole of each finger was sampled, but with the majority one swab was used for the thumb and all the fingers of each hand.

Contamination of Clothing.—Sweep plates were employed (Blowers and Wallace, 1955) to sample the clothing, each plate being made to traverse the whole length of two adjoining areas on each garment. In the case of the handkerchief, it was bunched up and pressed down on the agar

surface. The only pocket sampled was that in which the handkerchief was kept (in the case of women the handbag), and for this purpose a broth-moistened swab was rubbed about in the depths. In some surveys press plates were used —that is, contact between the cloth and the surface of the medium was made by means of a circular wooden slab, slightly smaller in diameter than that of the culture plates, giving an area of 50.2 sq. cm.

Dispersal of Organisms from Skin and Clothing

The cubicle employed in these experiments was tubular, consisting of plastic curtain material hanging from a hoop 3 ft. (91 cm.) in diameter. The hoop itself was filled in with transparent plastic, but had a slit in the centre through which the head of the subject could protrude. There was another slit which could be closed by clips down the side of the cubicle through which the subject entered. The whole arrangement was suspended by guy ropes from a rod supported on a large stand (see Fig.).

Cubicle employed in the experiments. The position of the four culture plates exposed in each experiment are shown on right.

The culture plates were exposed on each side of the subject at about 15 in. (38 cm.) from the ground. Only four plates were employed, experience having shown that larger numbers, such as were used by Hare and Thomas (1956), are unnecessary. Experience has also shown that, except when a carrier is actually exercising in the cubicle, *Staph. aureus* is not likely to be isolated on the exposed plates, and for this reason control estimations of the bacterial contamination of the air with the carrier standing still were not carried out.

The carriers exercised in the cubicle for 15 minutes by marking time and waving their arms about while wearing their ordinary everyday clothing. An attempt was made to use a uniform degree of violence, but this proved difficult.

Both the total number of colonies and those consisting of *Staph. aureus* on the exposed plates were counted, and, assuming that each colony develops from one organism, the results were expressed as the number of organisms falling on 1 sq. ft. (0.09 sq. m.) in one minute.

During November and December, 1956, nasal swabs were taken from 76 technicians, surgical dressers, and final-year medical students. *Staph. aureus* was isolated from 30, giving a carrier rate of 39.4%. Nineteen of these carriers and 12 of the non-carriers were employed as subjects for this investigation.

Contamination of Skin and Clothing

The results obtained in surveys of 15 carriers are given in Table I and show that six (Cer, Ans, Mas, Dle, Ler, Ham) had much less contamination of the skin or clothing than the remaining nine. The latter had *Staph. aureus*, sometimes in considerable numbers, on the skin and usually on sites having fairly direct contact with the nose—that is to say, the face, palms, and fingers. The forearms, probably because they are protected by the sleeves, were seldom contaminated, as, contrary to what is usually supposed, were the wrists. The hair, chest, abdomen, back, and legs were either free or the numbers were small.

The only item of clothing likely to have direct contact with the nose is the handkerchief, and this was usually contaminated heavily. So, too, was the pocket in which it was kept, but staphylococci could also be found on one or other site on the remainder of the clothing, and certainly on that of the front of the body.

There seems to be no doubt that the skin and clothing may continue to be contaminated for months, but whether its intensity varies greatly from day to day was not specifically investigated.

Contrary to expectation there was no correlation between the number of *Staph. aureus* in the nose and the intensity and extent of skin or clothing contamination. Carriers Dle and Ham, for example, had many in the nose but few on their persons, whereas the opposite was the case with Bit and Ell. Nevertheless, if the carriers studied be considered representative of carriers in general, there is no doubt that about three-fifths evidently have enough *Staph. aureus* on various sites of skin and clothing to render them capable of acting as donors of infection.

Source of the Staph. aureus on Skin and Clothing

Following the work of Gillespie, Devenish, and Cowan (1939), Miles, Williams, and Clayton-Cooper (1944), and Williams (1946), it is now assumed that most of the *Staph. aureus* found on skin and clothing are not multiplying there, but are derived from the individual's own anterior nares. Phage-pattern determinations, carried out for us by Dr. Patricia Jevons of the Central Public Health Laboratory, would suggest that with 12 of the 15 carriers this may well have been the case. For the majority of the skin and clothing strains isolated in the surveys carried out over the period December–April had the same pattern as those in the carrier's nose. Of the remaining three carriers, two (Ham, Cer) had staphylococci on the skin or clothing which were different from the nasal strain, but so few were actually isolated that they may have been environmental strains.

This leaves one carrier (Bit) who had no staphylococci in his right nostril when examined on February 14 and only 10 colonies on a plate from the left nostril. One of these colonies had the phage-pattern 52/80. This strain was also found on his face and his left forearm. On the other hand, one colony from each of the other areas—chest, abdomen, leg, left and right palms, one finger of his right hand, shirt, front and back of his coat, socks, and handkerchief—all had the pattern 55/71.

Widespread contamination of Bit, who is a healthy individual with no pyogenic or other lesions of the skin and only a few *Staph. aureus* of a different phage pattern in one nostril, made it appear probable that this organism was derived from some situation other than his nose, where there was sufficient warmth and moisture to enable the organism to multiply. No *Staph. aureus* was isolated at preliminary examinations on May 15 and July 17 from the axillae, but large numbers were obtained from the perineum. It should perhaps be added that there was so heavy a growth of coagulase-negative skin micrococci from the latter area that, without the assistance afforded by the phenolphthalein diphosphate medium, the colonies of *Staph. aureus* might have been missed.

In view of this, a much more detailed survey was carried out on July 25, the results being as follows (the figures give the total number of *Staph. aureus* colonies isolated from

TABLE I.—*Presence of Staph. aureus on Skin and Clothing of 15 Nasal Carriers*

Name	Sex	Date	Left Nose	Right Nose	Hair	Face	Chest	Abdomen	Back	Legs	Left Forearm	Right Forearm	Wrists	Left Palm	Right Palm	L. Hand: Thumb	L. Hand: Finger 1	L. Hand: Finger 2	L. Hand: Finger 3	L. Hand: Finger 4	R. Hand: Thumb	R. Hand: Finger 1	R. Hand: Finger 2	R. Hand: Finger 3	R. Hand: Finger 4	Front Coat	Back Coat	Shirt	Trousers	Socks	Handkerchief	Handkerchief Pocket
Ale ..	M	Feb. 6	∞	∞	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	200	150
		Apr. 4	∞	∞	0	1	0	0	0	–	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	21	3	3	31	0	∞	∞
		June 25	∞	∞	0	∞	0	0	0	–	–	–	0	2	0	←		9		→	8	6	0	16	1	11	3	0	1	3	100	∞
Son ..	M	Dec. 12	∞	∞	1	6	0	0	5	0	–	–	0	–	–	←		2		→	←		1	–	→	0	4	0	0	3	1	15
		Feb. 13	∞	∞	2	20	0	0	0	2	1	–	–	0	50	←		2		→	←		2	–	→	1	1	0	6	0	13	4
		June 27	∞	∞	0	20	0	0	0	0	–	–	0	0	8	←		0		→	3	1	4	∞	30	7	1	0	2	0	17	11
Ray ..	M	Nov. 27	∞	∞	0	1	1	0	1	1	–	–	–	–	–	–	1	2	2	–	–	2	1	1	–	3	1	4	3	0	100	100
		Jan. 31	∞	∞	1	8	2	0	0	0	–	–	0	–	–	–	0	5	1	–	–	2	15	2	–	0	4	0	3	1	100	38
Ips ..	M	Feb. 12	32	35	1	8	3	0	0	1	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0	3	1	0	5	0	7	3
		June 26	100	∞	0	2	0	50	0	0	2	0	0	0	1	←		1		→	0	5	50	0	0	5	2	1	0	3	2	6
Ell ..	F	Feb. 6	0	100	0	2	–	–	–	0	0	0	0	0	1	1	0	0	1	0	1	0	1	1	3	1	0	–	2	–	20	–
		June 26	150	25	0	26	–	–	–	–	0	0	0	–	14	←		21		→	100	cont.	150	4	0	0	0	0	1	–	–	26	100
Ret ..	F	Feb. 6	0	100	0	0	–	–	–	0	0	0	0	0	0	0	100	1	0	0	0	4	0	0	0	2	0	–	0	–	20	–
Ett ..	M	Feb. 19	200	∞	6	11	40	3	0	30	26	4	23	40	15	←		100		→	←		1	–	→	2	3	2	4	11	16	12
		Aug. 27		∞	0	60	3	3	–	0	0	1	–	–	–	←		100		→	←		1	–	→	22	2	0	20	–	–	–
Ade ..	M	Feb. 5	∞	∞	1	27	0	0	0	1	2	0	2	0	0	2	0	3	2	3	8	5	36	4	0	0	3	1	1	0	500	17
		July 8	∞	∞	0	0	0	0	0	1	–	–	0	0	5	←		9		→	1	30	9	0	0	0	0	0	0	0	3	2
Bit ..	M	Feb. 14	10	0	0	2	3	13	0	2	4	0	0	4	1	←		9		→	←		2	–	→	5	4	1	0	15	1	0
		July 25	0	0	0	0	0	2	0	0	0	0	0	0		0	4	0	0	0	0	0	0	0	0	0	0	5	8	2	0	0
Cer ..	M	Dec. 19	∞	∞	4	0	0	5	0	0	–	–	3	–	–	←				9	→				→	1	8	0	0	1	3	2
Ans ..	M	Feb. 11	50	70	0	0	0	0	0	0	0	0	0	17	0	0	0	0	0	0	0	0	0	0	0	0	2	4	1	0	0	0
Mas ..	M	Feb. 7	∞	∞	0	0	0	0	0	0	0	0	0	–	–	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	4	0
Dle ..	F	Dec. 12	∞	∞	0	1	1	–	0	–	–	–	0	–	–	←				9	→				→	0	0	0	0	0	6	0
		Jan. 27	∞	0	0	0	0	0	0	0	0	–	–	0	0	←		0		–	0	0	0	0	0	0	0	0	1	0	0	0
		Feb. 13	∞	∞	0	0	0	0	0	–	–	2	0	0	0	←		0		→	←		0	–	→	0	0	–	6	–	2	0
Ler ..	M	Feb. 11	∞	50	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0
		June 27	∞	∞	0	19	0	0	0	0	0	0	0	0	1	←		7		→	0	2	0	0	3	1	0	0	0	0	4	2
Ham ..	M	Nov. 30	∞	∞	0	0	0	0	3	0	–	–	1	–	–	–	0	0	0	–	–	0	1	0	–	0	0	3	0	0	1	2

Note.—The figures give the number of colonies of *Staph. aureus* isolated from each area. The symbol 0 means that no *Staph. aureus* was isolated, and – indicates no test. In the case of women, the skirt was sampled instead of the trousers, and blouse or pullover in place of shirt. The handbag was sampled instead of the pocket.

approximately 16 sq. cm. of skin by a moistened swab, or on 50.2 sq. cm. of clothing using press plates):

Staph. aureus of Phage Pattern 3C/55/71 Present.—Abdomen (L 1, R 1). Perineum, 150. Fold between scrotum and thigh (L 1,000, R 100). Penis, 1. Front scrotum, 4. Inner thigh (L) 15. Foot: dorsum (L 4, R 1); sole (L) 1. Forefinger (L) 4. Drawers: front (L 3, R 4); inside leg (L 100, R 4); seat (L 47, R 8). Shirt, upper front (L 1, R 4); lower front, 14; sleeve (L 3, R 3); upper back, 3. Trousers, leg (L 2, R 4). Socks (L) 2.

No Staph. aureus Present.—Nostrils (L and R); throat; hair; chest (L and R); axilla (L and R); umbilicus; back (L and R); groin (R); inner thigh (R); outer thigh (L and R); anal fold; leg (L and R); foot, sole (R); forearm (L and R); wrist (L and R); hand, back (L and R), palm (L and R); R thumb and fingers; L thumb and 2, 3, and 4 fingers; faeces; coat; socks (R); handkerchief.

Staph. aureus of phage pattern 52/80 was found on the left groin and lower back, upper back, and left sleeve of the shirt.

On this occasion no *Staph. aureus* was isolated from either nose or throat, but colonies belonging to the same phage pattern as those found in February were obtained from many areas, by far the largest number coming from the perineum and the folds between the scrotum and thighs. The neighbouring areas—that is, the front of the scrotum, the penis, the anal fold, the skin of the inner part of the thighs about 4–6 in. (10–15 cm.) from the perineum, the area over Poupart's ligament, the lower part of the abdomen, and the umbilicus—were either free or much less heavily contaminated. The clothing in apposition to the perineum, such as the legs and seat of the drawers, was heavily contaminated, whereas more distant areas had much fewer organisms.

There was no evidence that the perineum had been contaminated by *Staph. aureus* coming from the faeces. Not only was this organism not found in a sample of faeces, but, as already mentioned, it was not isolated from a swab rubbed along the anal fold and over the anus. *E. coli*, it may be added, was present in fair numbers on this area.

These investigations suggest that the perineum of this particular individual had been the primary source of the *Staph. aureus* on his skin and clothing all along. This implies that this organism was able to multiply on this area of the body. An experiment carried out on July 30 would suggest that such is the case.

The subject defaecated at 8 a.m. and then at 11 a.m. thoroughly washed the whole of the perineum, inner side of the thighs, anal fold, testicles, and penis with soap, using many changes of warm water in a bowl. The area was dried with a sterile towel. He then put on a clean shirt, drawers, and trousers, and went about his work in the usual way, much of it involving sitting at a bench. The weather was warm and humid, so that there was much sweating. That night he put on clean pyjamas and slept between clean sheets. He did not defaecate again until 8 a.m. next day, and great care was taken to avoid touching the perineum or neighbouring areas during the intervening period.

Swabs moistened with broth were employed to take samples from the perineum and adjacent areas immediately after washing and again after 4, 7, 12, and 24 hours. Only a few micrococci and no *Staph. aureus* were isolated from swabs taken after washing; but both organisms, and particularly the micrococci, were present in increasing numbers in the samples taken after four and seven hours. By the 12th and the 24th hour there were so many micrococci that a heavy confluent growth was obtained, but embedded in it were many phosphatase-positive colonies of *Staph. aureus*. The results so far as they concern *Staph. aureus* are given in Table II.

TABLE II.—*Growth of Staph. aureus on the Perineum of Subject Bit*

Time	No. of *Staph. aureus* isolated from: Folds between Thigh and Scrotum: Left	Folds between Thigh and Scrotum: Right	Perineum	Anal Fold
After washing	0	0	0	0
4 hours	96	4	1	0
7	360	160	16	0
12	640	800	176	0
27	1,200	1,200	600	0

Specimens of faeces taken before the experiment and at the 22nd hour were both negative.

A somewhat similar increase in the number of *Staph. aureus* on the skin following removal of most of the surface organisms by washing was observed by Devenish and Miles (1939) in their studies of the flora of the hands during operations. They suggested that the staphylococci were already present in the sweat glands and deeper layers of the skin, and that sweating induced by wearing rubber gloves merely carried them to the surface. It is improbable that this is the explanation for our results. Table II shows, for example, that the numbers present as long as four hours after washing were not very large. In this experiment no attempt was made to promote sweating, but in another in which it was induced by sitting on a space heater for one and a half hours after washing, only 11, 0, and 7 colonies of *Staph. aureus* were obtained from the three areas at the end of that time.

It would therefore seem that *Staph. aureus* was actually multiplying on the perineum of subject Bit. For all practical purposes he was a perineal carrier of this organism, he had been one for several months, and organisms from this reservoir were able to reach other sites on the skin and clothing to much the same extent as with nasal carriers.

Dispersal of Staph. aureus into Free Air as a Result of Movement

With the use of the new form of cubicle illustrated above, in which the head of the subject is outside, the ability of 13 non-carriers and 19 carriers to disperse *Staph. aureus* was investigated. The results obtained with the non-carriers are given in Table III. Very few staphylococci appeared on the plates, the highest number falling on 1 square foot (930 sq. cm.) in one minute during exercise being 1.

TABLE III.—*Dispersal of Staph. aureus by Subjects Without Staph. aureus in the Nose*

Name	Sex	No. of Organisms Falling on 1 sq. ft. in One Minute	
		Total	*Staph. aureus*
Nes	M	484	1·0
Obs	F	55	0·8
Ris	M	340	0·4
Ple	M	135	0·2
Jed	F	294	0·2
Ink	F	39	0·2
Eel	M	115	0·2
Ael	M	350	0·2
Eek	M	47	0·0
San	F	65	0·0
Eld	M	771	0·0
Vis	M	96	0·0
Cis	F	72	0·0

The results obtained with 19 known nasal carriers are given in Table IV. Six dispersed either no *Staph. aureus* at all, or less than 1 per square foot per minute. They were therefore in the same category as individuals who are not carriers. The counts obtained with the remaining 13 were higher, and for this reason all must be looked upon as potentially more dangerous than the rest of the population. Nevertheless, it is obvious that some were much more so, and no fewer than seven produced counts of 5 or more *Staph. aureus* per square foot per minute on at least one occasion.

Tests carried out at intervals over several months showed that some carriers, such as Ale, dispersed large numbers on each occasion, but others were much more variable. No adequate reasons for this variation can be advanced, but factors such as type of clothing worn, and the time elapsing between the last bath or change of underwear and the tests, may play an important part. Lower counts were certainly obtained with four carriers when "best clothes" were worn (see Table V).

Since the dispersed organisms must have come from either skin or clothing, it might be assumed that individuals with

TABLE IV.—*Dispersal of Staph. aureus by Known Nasal Carriers of this Organism*

Name	Sex	Date	Growth on Nasal Swabs		No. of Organisms Falling on 1 sq. ft. in One Minute	
			L	R	Total	*Staph. aureus*
Ale	M	Jan. 8	∞	∞	153	2·4
		Feb. 6	∞	∞	372	10·6
		April 4	∞	∞	494	27·8
		June 25	∞	∞	565	18·0
Son	M	Feb. 13	∞	∞	431	4·6
		April 3	∞	10	520	9·4
		June 27	∞	∞	284	1·0
Ray	M	Jan. 22	150	∞	193	10·8
Ade	M	Jan. 7	150	20	247	5·6
		Feb. 15	∞	∞	120	1·6
		March 21	150	∞	64	1·0
		May 30	∞	∞	N.D.	4·0
		July 11	∞	∞	302	7·8
Ans	M	Jan. 23	300	1	1,133	1·2
		Feb. 11	50	70	93	1·6
		April 4	4	20	520	1·6
Eal	M	Jan. 22	50	300	892	2·2
		May 31	1	0	885	6·5
Ips	M	Feb. 12	∞	∞	179	2·6
Ell	F	Jan. 21	300	300	127	1·2
		Feb. 6	100	0	216	1·2
		June 26	150	25	1,145	6·4
Bit	M	Feb. 14	0	10	276	4·5
		July 25	0	0	124	2·8
Cer	M	Jan. 17	100	300	172	1·4
Ett	M	Jan. 8	300	300	53	1·1
		Feb. 19	∞	200	169	1·0
Mas	M	Jan. 14	300	300	223	0·4
		Feb. 7	∞	∞	350	0·8
		July 8	∞	6	819	10·2
Dle	F	Feb. 13	∞	∞	389	0·6
		June 27	∞	0	279	0·0
Ean	F	Jan. 15	250	300	153	0·4
Per	M	Jan. 24	3	3	93	0·4
Lin	M	Jan. 15	100	20	152	0·4
Ham	M	Jan. 22	100	300	216	0·0
Ret	F	Feb. 6	100	0	38	0·0
Ler	M	Feb. 11	∞	50	488	0·0
		June 27	∞	∞	664	2·0

TABLE V.—*Dispersal of Organisms While Wearing Different Types of Clothing*

Carrier	Wearing Working Clothes		Wearing Best Clothes	
	Total Organisms	*Staph. aureus*	Total Organisms	*Staph. aureus*
Bit	276	4·5	169	2·9
Son	431	4·6	312	3·2
Ray	193	10·8	152	2·5
Ade	302	7·8	164	0·6

heavy surface contamination would disperse more organisms. Many of the dispersal experiments were carried out on the same days as the surveys, and comparison between Tables I and IV will show that, on the whole, there was correlation between numbers dispersed and extent of surface contamination. Nevertheless, there were obvious exceptions. One carrier—Ett, for example—was heavily contaminated on each of two occasions, but, probably because he was the most lethargic individual in the cubicle we have encountered, his counts were so low that he could hardly be described as a disperser at all.

On the other hand, there was very little correlation between the number of *Staph. aureus* in the nose and ability to disperse. Two carriers—for example, Dle and Ler—had large numbers in the nose but dispersed no *Staph. aureus* at all, or only a few. Another two, Eal and Bit, had very few in the nose, but the former produced a count of 6.5 and the latter 4.5. The same individual, too, might have approximately the same number in the nose on two occasions when very different results were obtained in the dispersal experiments—for example, Ade and Son.

Source of the Dispersed Organisms

Comparison between the phage patterns of the dispersed organisms and those present in the nose of the same individual in the experiments carried out during the period December–April showed that, excluding three carriers who dispersed none at all (Ler, Ret, and Ham), the pattern was the same in 14 out of the remaining 16. Thus in these instances the primary source of the dispersed organisms may well have been the nose.

Of the remaining two, one (Dle) dispersed only three colonies, which were different from each other and from those in the nose; the second (Bit) was the perineal carrier already referred to. The strains he dispersed on February 14 and July 25 were of the same phage pattern (3C/55/71) as those on the perineum and clothing. They were therefore different from the strain (52/80) which was present in his nose. It is thus obvious that *Staph. aureus* derived from some primary source other than the nose may be dispersed during exertion as readily as when the primary source is the nose.

Discussion

Although nasal carriers have been looked upon for some time as constituting one of the most important reservoirs of *Staph. aureus* in the community, it is still not known whether all carriers can transmit their organisms to others with equal facility. This is partly due to the fact that very little is still known about the mechanism by which transmission occurs, but from the work of Duguid and Wallace (1948) and Hare and Thomas (1956) it would seem that it occurs by a comparatively circuitous route, the first and most important part being contamination of the skin and clothing of the carrier himself.

Detailed surveys, using numerical methods, were accordingly made of the skin and clothing of nasal carriers of *Staph. aureus*, and these showed that about two-thirds had sufficient numbers of this organism on different sites to render them capable of acting as donors. Some were more heavily contaminated than others, but until much more information is available it is not possible to suggest a line of demarcation between the really dangerous and the less dangerous carrier.

Even so, it is obvious that the number of staphylococcal carriers amongst hospital populations who are likely to have sufficient *Staph. aureus* on various parts of their skin and clothing to enable them to act as donors is considerable. To make matters worse, it is probably even larger than has previously been thought. For evidence has been obtained that some apparently normal individuals may possess areas of skin, such as the perineum, on which *Staph. aureus* can multiply. They may have no staphylococci at all in their nose, or, if they are present, they may be of an entirely different phage pattern. Nevertheless, the organisms from the primary site on the skin can reach areas of skin or the clothing at some distance, and be dispersed during movement in the same way as with individuals whose organisms have come from the nose. Such individuals, therefore, are potentially as dangerous as the nasal carrier.

They may be even more dangerous, for in the paper by Hare and Thomas reference was made to a subject, Pri, whose skin and clothing were heavily and widely contaminated and who dispersed more *Staph. aureus* when exercising (47.4 per sq. ft. per minute) than any of the carriers studied in this paper. The phage pattern of the dispersed organisms was 53, and although he had *Staph. aureus* in his nose they had the phage pattern 29. The primary source of the dispersed organisms was never ascertained, and although it may have been the perineum, as seems to have been the case with the subject investigated in this paper, it is quite possible that other sites, such as the axillae, umbilicus, or even the hands, may be similarly parasitized.

It is thus evident that it is no longer justifiable to assume that only nasal carriers need to be considered when attempts are made to trace the donors during outbreaks of infection. Much more extensive investigations are obviously required.

Nor can it be assumed that most of the *Staph. aureus* found on the skin or clothing, or which are dispersed into free air during movement, have invariably come from the individual's own nose. For this reason, wholesale instillation of antiseptics or antibiotics into the noses of carriers may eradicate part of the reservoir of *Staph. aureus* in hospital communities, but is unlikely to have much effect on that part of the reservoir constituted by those whose *Staph. aureus* are derived from some non-nasal site.

Summary

Extensive surveys of the skin and clothing of nasal carriers of *Staph. aureus* have shown that about three-fifths have sufficient numbers of this organism on certain areas, particularly the hands and the clothing of the front of the body, to enable them to transmit their own organisms to other persons with whom they come into direct physical contact, by means of objects such as blankets or towels which they have touched, or as a result of dispersal into free air during movement.

With many carriers, the primary source of these organisms is the nose, but the number of *Staph. aureus* in nasal swabs gives little indication of the extent of skin and clothing contamination, or ability to disperse this organism. Nevertheless, at least one individual in the series studied in this paper had a primary source which was not in the nose but on the skin of the perineum. *Staph. aureus* from this area could contaminate the skin and clothing and be dispersed during movement to much the same extent as with nasal carriers.

Thus, when possible sources of infection are being sought, the existence of non-nasal carriers of *Staph. aureus* must not be overlooked.

Our thanks are due to Dr. R. E. O. Williams and Dr. Patricia Jevons, of the Central Public Health Laboratory, Colindale, for the determinations of phage pattern of the staphylococci.

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The establishment of air pollution advisory councils in all countries and legal enforcement of measures to prevent air pollution were recommended by a W.H.O. expert committee on air pollution recently. The committee's meeting was W.H.O.'s first attempt to marshal the facts of air pollution and to establish a programme for preventive and remedial action by national authorities. According to the committee, it was certain that on the basis of existing knowledge much pollution could be avoided at a reasonable cost by careful planning and siting of factories and dwellings, better design of equipment, and better operation based on adequate training of management and employees. With small domestic heating appliances it was not so far economically practicable to burn coal without considerable emission of smoke, and to avoid air pollution new heating systems might have to be introduced into some communities. The committee noted that two processes for removing more than 90% of the sulphur dioxide from the chimney gases had been in use over several years at power stations in England. The cost of the processes was still very high, but experiments were in progress in several countries to find cheaper and more satisfactory systems.

ACQUISITION OF STAPH. AUREUS BY NEWBORN BABIES IN A HOSPITAL MATERNITY DEPARTMENT

BY

JOSEPHINE COOK, M.B., D.C.H.

J. A. PARRISH, M.B., M.R.C.P.

AND

R. A. SHOOTER, M.D.

From the Children's Department and Department of Bacteriology, St. Bartholomew's Hospital, London

In hospital nurseries it has been repeatedly found that *Staphylococcus aureus* can be isolated from the noses of practically all newborn babies during the first two weeks of life (Cunliffe, 1949; Barber, Wilson, Rippon, and Williams, 1953). The way in which staphylococci spread in nurseries is unknown, although it has been shown that babies are not often colonized by their mother's staphylococci (Rountree and Barbour, 1950; Ludlam, 1953; Barber *et al.*, 1953).

The present investigation was an attempt to throw some light on the routes by which staphylococci spread in the infants' nurseries in this hospital. We began with the knowledge that virtually all our full-term babies acquired staphylococci in their noses in the first few days of life, and we hoped that, by excluding in turn each component of the babies' environment which might be responsible for contamination with staphylococci, we might be able to trace at least some of the normal routes of spread.

It does not necessarily follow that staphylococci causing clinical infection spread by the same routes as those responsible for symptomless colonization of the nose, but it is reasonable to think that some of the routes may be the same. If this is so, discovery of normal routes of staphylococcal spread might assist in devising measures for the control of spreading staphylococcal sepsis.

Methods

The Nurseries.—One of the two nurseries involved was a large airy room (34 by 21 by 12 ft.; 10.4 by 6.4 by 3.7 m.) containing 11 cots, each cot being approximately 2 ft. (60 cm.) from its neighbour. The other nursery, although considerably smaller (10 by 21 by 12 ft.; 3 by 6.4 by 3.7 m.) held the same number of cots, spaced approximately 1 ft. (30 cm.) from each other.

Babies.—All babies coming to the nurseries were full-term and breast-fed, being taken to their mothers. Where breast-feeding did not become established, the baby was nevertheless put to the breast four-hourly. Babies and mothers normally went home on the 14th day.

Staff.—The permanent nursing staff consisted of between 7 and 9 midwives, with at any one time about 7 junior nurses. The babies might be visited by any of 12 members of the medical staff and approximately 10 students, but only 5 of these 22 people were normally likely to handle them.

Nursing Procedures.—Babies were bathed at birth. Thereafter the face and nappie area were washed in water, but the whole baby was not bathed until the 13th day. From the third morning they were oiled all over with liquid paraffin. No masks or gowns were worn by nurses as a routine, and a bactericidal hand cream was not used.

Bacteriology.—Noses were examined by rubbing dry cotton-wool swabs six times round the inside of each nostril. Cultures were made on 5% horse-blood-agar plates, and this medium was also used for other cultures, except in the case of stools, which were inoculated on to 8% salt agar plates. Bedding and gowns were examined by the sweep-plate method (Williams, quoted by Blowers and Wallace, 1955). Staphylococci which coagulated plasma in a tube were regarded as *Staph. aureus*.

Carriage of Staph. aureus

Nasal swabs were taken daily, with the occasional exception of Sundays, from 53 newborn babies. By the 10th day all the babies had staphylococci in their noses, and the rate at which they acquired them is given in the Table (see "control"). Forty-four stools from 12 babies were examined: 23 of these specimens contained staphylococci, and with one exception all the babies were found at some time to be positive. The negative baby was discharged home after only six days.

Nasal Carriage of Staph. aureus by Newborn Babies. Babies Becoming Carriers on Successive Days of Life

Day of Life	Control	Chlorhexidine	Gown	Individual Gown	Triple Dye	Individual Gown and Triple Dye
1	1	—	1	—	4	—
2	9	4	2	1	1	1
3	8	2	2	3	2	6
4	16	5	3	3	5	3
5	6	4	11	3	3	5
6	4	3	4	4	5	2
7	5	8	2	3	9	1
8	3	—	4	2	5	—
9	—	1	1	1	—	1
10	1	—	2	1	2	1
11	—	—	1	1	1	1
12	—	1	—	—	1	1
Babies still negative on 12th day	—	3	2	7	17	8
Total	53	31	35	29	55	30
Median day	4	6	5	7	7	5

Role of Bedding.—Blankets from 16 babies were examined daily, and in each case the blankets were found positive before the baby's nose. The number of staphylococcal colonies per sweep-plate varied from 1 to 73 from any one blanket. Each new baby started with fresh blankets, but conventional laundering is known not to rid blankets of staphylococci. Sixteen blankets returned from the laundry were examined: eight were found to carry staphylococci. In view of this it was decided to see the effects of nursing 10 babies in sterilized bedding. After birth these babies were placed in cots containing autoclaved bedding, and when any changes were required the bedding was replaced with sterile bedding. This procedure, which could be used only on a limited experimental scale because it damaged the blankets, was continued until the baby became a nasal carrier. All 10 babies became carriers between the 2nd and the 10th day. In eight cases examination of the bedding on the first day failed to yield staphylococci, although for all but 2 of the 10 babies the bedding became positive before the baby. In the two exceptions the baby and the bedding were found to be positive for the first time on the same day. These results suggested that, although babies might acquire staphylococci from their bedding, the bedding was not in the first instance responsible.

Role of Staff.—Staphylococci might spread directly from the staff to babies in several ways. Babies must be handled, and they are frequently in contact with the nurses' clothes. To try to block the passage of staphylococci from attendants to babies, a trial was begun which involved 95 babies. One feature common to all the babies was that two months before the trial began chlorhexidine ("hibitane") hand-cream (1% in a water-miscible base) was placed at wash-basins, and those who handled the babies were asked to use the cream every time they washed their hands. With chlorhexidine cream as the only departure from normal practice 31 babies were watched in three months. Twenty-nine

of them were carriers by the end of their stay in hospital, and for the first time in this examination two babies left the hospital not carrying staphylococci in their noses (see Table), and three were free from staphylococci after 12 days.

Staff Gowns.—In addition to the hand-cream babies, a further 35 babies were looked after by nurses and medical staff wearing gowns over their usual uniforms. These gowns were clean daily, but no attempt to confine one gown to one baby was made. Once on, the gown might be worn by a nurse during the toilet of several babies. This procedure had the same effect as chlorhexidine hand-cream alone, two of the babies being free from staphylococci at 12 days. A possible explanation for the lack of effect of the gowns was that the practice of attending to several babies wearing the same gown meant that a baby might get from the gown staphylococci deposited there by preceding babies. Support for this idea was obtained by examining gowns in the nursery during the late afternoon on five days. *Staph. aureus* was isolated from 11 of the 18 gowns examined. The obvious alternative was to provide each baby with its own attendant's gown. This scheme had the drawback that while a nurse was handling a baby she was unable to respond to any other calls without first taking off the gown, but it was carried out for 29 babies. The results (see Table, "individual-gown" babies) suggested that the gown was of some value in addition to the hand-cream, as 7 of the 29 babies were free from staphylococci at 12 days. It should be made clear that, while a general measure, such as the use of hand-cream, related to all babies, it was not possible to use gowns for all the occupants of a nursery at once. During the trials of gowns, therefore, the nurseries contained babies attended to with gowns and babies nursed normally.

Role of the Umbilical Cord.—Jellard (1957) confirmed other authors' reports of the frequency with which umbilical cords are colonized by *Staph. aureus*. She suggested that cords might be a source from which staphylococci could spread, and claimed that by treatment of the umbilical cord with triple dye the spread could be reduced. We have used this method for 55 babies. At birth triple dye* was painted on and around the umbilical cord, and thereafter every morning until separation took place. The cords were left uncovered. Of these 55 babies, 17 were still not nasal carriers of staphylococci on the 12th day.

Combination of Individual Gowns and Triple Dye.—As individual gowns and triple dye both appeared to be in some degree effective in preventing colonization of babies' noses, it was decided to try the effect of both methods combined. While this was being done, all the babies in the nursery were treated with triple dye, but, as before, only two at a time were nursed with individual gowns. Of 30 babies, 8 were free from staphylococci in their noses after 12 days.

Mothers and Babies

We did not at first look to see if there was any relation between staphylococci in babies' and mothers' noses in view of other workers' repeated findings to the contrary. It was, however, possible that some of the measures taken had altered the situation, and that babies might now be obtaining their mother's nasal staphylococci. We did not find this to be so. Fifty mothers with 51 babies provided 21 pairs where both mother and baby were nasal carriers. Of these, in 10 cases the staphylococci differed in their sensitivity to antibiotics; of the other 11 pairs, in 9 cases the phage types were different. Two pairs had the same phage types, but in each case the baby was carrying another staphylococcus with a different antibiotic sensitivity. Additional proof was that for 24 pairs the baby was a nasal carrier while the mother was not.

If babies are not commonly infected with their mother's nasal staphylococci, it is possible that they obtain staphylococci from the area with which they are in closest contact—the breast. To test this, 20 mothers and babies were examined daily (gowns and chlorhexidine hand-cream were not in use). In nine cases the baby became a nasal carrier before staphylococci were isolated from the mother's breast, in seven staphylococci were isolated for the first time from mother and baby on the same day, and in four staphylococci were recovered from the mother before the baby.

This suggested that the baby might be responsible for depositing staphylococci on the breast, as suggested by Duncan and Walker (1942), and sensitivity testing showed that in most cases the baby's nasal staphylococcus and the mother's breast staphylococcus were alike. Phage-typing confirmed this, as of eight pairs examined six were of the same phage type.

Sepsis.—There was no obvious epidemic of sepsis amongst the babies during this investigation. *Staph. aureus* was isolated from such lesions as whitlows, septic spots, or sticky eyes in 35 of 541 babies. There were in addition 40 babies with septic lesions from whom either swabs were not taken (18 babies) or from whom staphylococci were not isolated (22 babies).

Throughout the investigation no evidence was obtained that the carriage rate differed in the two nurseries.

Discussion

As it appeared that all our babies were colonized by staphylococci during their stay in hospital, this investigation was begun in the optimistic hope that, by blocking one or more routes by which staphylococci might spread, colonization could be prevented and the route identified.

Babies must be handled, and Murray and Calman (1955) used chlorhexidine cream to eliminate staphylococci from the hands of attendants. In our case this measure had some effect, seeing that of 31 babies 3 were still free from staphylococci in their noses on the 12th day. This rate was not improved on when the nurses wore gowns, probably because the babies seen to first left their staphylococci on the gowns for those dealt with later. The solution to this difficulty was to use one gown for one baby, and in this way 7 of 29 babies reached the 12th day free from staphylococci.

If this suggested that a proportion of babies acquired staphylococci from their attendant's hands or clothes, the reduction in nasal carriage by painting the umbilical cord with triple dye was presumably due to a different mechanism, and indicated the importance of the umbilical cord as a breeding-ground for staphylococci.

The final experiment in which individual gowns and triple dye to umbilical cords were used together showed that the two methods in combination were no better than each method by itself in preventing colonization of the babies' noses by the 12th day (see Table).

It is tempting to suggest from this that babies differ in their susceptibility to staphylococci and that the proportion of babies protected from staphylococci by either triple dye or individual gown represents the same proportion of babies—that is, those with a slightly greater resistance to staphylococci. Combination of the two methods may again only have picked out the same proportion of babies.

Looked at in another way, it suggests that perhaps about three-quarters of our babies acquired their staphylococci in some other way than direct from their attendants. This route we have not yet been able to identify. From a total of 420 c.ft. (11.9 cu.m.) of air examined in the course of eight months we isolated 22 colonies of *Staph. aureus*, and further work may show that aerial spread plays a significant part in the dissemination of staphylococci in our nurseries.

In agreement with other authors, no evidence was obtained that mothers were the source of their offspring's staphylococci, and, in fact, there was a strong suggestion that mothers' breasts acquired staphylococci from the babies. If this is so it would explain why staphylococci isolated from breast abscesses of mothers delivered in hospital are usually resistant to penicillin, although the mother herself may not have become a nasal carrier of a hospital antibiotic-resistant organism.

*Triple dye = brilliant green 2.29 g., proflavine hemisulphate 1.14 g., crystal violet 2.29 g., water 1,000 ml.

Summary

An investigation amongst full-time newborn babies in two nurseries has been carried out in an attempt to discover the usual routes of spread of *Staph. aureus*.

Initially 53 babies were all found to be nasal carriers by the 10th day, and 11 out of 12 of these babies also carried staphylococci in their stools. Examination of bedding suggested that this was not the immediate source of staphylococci, and prevention of possible contamination from the staff by the use of chlorhexidine hand-cream or gowns made little difference.

The use of triple dye to the umbilicus and individual gowns for each baby, both as separate and as combined measures, produced a reduction in the nasal carriage rate on the 12th day of life by about 25–30%.

No evidence was obtained that babies gained staphylococci from their mothers, but there was evidence that staphylococci on the mothers' breasts came from their babies.

We would like to thank Dr. C. F. Harris and Mr. J. Beattie for permission to conduct these trials; we are also much indebted to the Sister in Charge of the Maternity Ward and her staff for their co-operation. Dr. R. E. O. Williams kindly carried out the phage-typing for us.

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MASKING AND GOWNING IN NURSERIES FOR THE NEWBORN INFANT

EFFECT ON STAPHYLOCOCCAL CARRIAGE AND INFECTION

BY

JOHN O. FORFAR, *M.C.*, M.B., F.R.C.P.Ed.
M.R.C.P., D.C.H.
Consultant Paediatrician, Edinburgh Northern Group of Hospitals; Senior Lecturer, Department of Child Life and Health, University of Edinburgh

AND

A. F. MACCABE, M.D., D.P.H.
Consultant Bacteriologist, Edinburgh Northern Group of Hospitals; Lecturer, Department of Bacteriology, University of Edinburgh

Reports from various parts of the world testify that staphylococcal infection of the newborn infant is a widespread problem in maternity units, a problem to which, unfortunately, no easy solution is apparent. There is general agreement that in the control of this infection prophylaxis rather than the treatment of established lesions is the prime objective. As a prophylactic measure masks and gowns are worn extensively if somewhat uncritically by attendant personnel. Between one maternity unit and another the practice of masking and gowning can vary considerably, from a strictly regulated conscientiously performed regime to a meaningless ritual or mere gesture.

This paper describes a controlled trial carried out in a maternity unit with the object of determining the effect of masking and gowning on staphylococcal carriage and infection of the newborn infant.

The Experiment

In a 50-bedded maternity unit over a period of three months two nurseries were set aside for a controlled experiment.

At birth babies were allotted at random to one of these two nurseries. In one nursery (the "masked" nursery) a strict masking and gowning regime was in operation, in the other (the "unmasked" nursery) no masks or gowns were worn. The attendant staff was common to both nurseries. In the masked nursery all personnel entering the nursery, whether doctors, nurses, or cleaners, donned a mask and gown. The masks consisted of four layers of gauze with a "cellophane" insert, and extended below the chin. The nursing staff changed their masks at least every hour. The masks were autoclaved in a drum and when required were removed from the drum with sterile forceps. The instructions were that while being worn the mask should not be touched at all by hand. On discarding, the masks were dropped into a lidded receptacle containing antiseptic. Gowns donned before entering the nursery were put on in an ante-room, where they were kept hanging when not in use. In addition to the gown worn on entering the nursery each cot carried a folded gown which was worn when the baby in that cot was being handled. All gowns were changed every 24 hours or when soiled. They were not autoclaved, but one stage of the laundering was to raise the temperature of the washing water to 200° F. (93° C.) for 10 minutes. In the unmasked nursery nurses wore their ordinary uniform, the apron of which was changed daily or when soiled.

For the first two days the babies were taken to their mothers for feeding. In the case of the babies from the masked nursery the mothers were masked and gowned with the baby's "individual" gown. Thereafter the mothers fed their infants in the nurseries, and again in the masked nursery they were appropriately masked and gowned. Mothers were permitted to handle their own babies only. If any baby developed an infection in either nursery he was immediately removed to an isolation nursery. The babies from the masked nursery were bathed in a bathroom kept for them only; those in the unmasked nursery were bathed in another bathroom. There was thus no direct contact between the babies from the two nurseries. Bathing was carried out daily from the fourth day onwards.

So far as possible other factors were kept constant in the two nurseries. The rule that hands should be washed between handling each baby applied in both. Daily cleaning, by wet mopping, was carried out in both. Temperature, floor space per cot, and ventilation were the same.

Between occupants cot clothing was dealt with as follows. The cot mattress was aired unless the baby had suffered from an infection. If so, the mattress was autoclaved. Blankets were washed at 90° F. (32° C.). Other cot clothing, mattress cover, canvas bassinet, sheet, wrap, gown, napkin, and cot cover underwent a stage in laundering in which they were washed at 200° F. (93° C) for 10 minutes.

Understandably the amount of traffic in the masked nursery was somewhat less than in the unmasked nursery, as the masking and gowning regulations in that nursery deterred entry for other than essential purposes. One other relevant factor was that this experiment was carried out at a time when a high infection rate for minor staphylococcal infection prevailed among the babies. This indeed was one of the considerations which prompted it. All infections in babies, no matter how trivial, were recorded, and, if possible, a swab was taken from the lesion. Each baby had an eye swab taken routinely on the fourth day, a nasal swab taken on the eighth day, and an umbilical swab taken at the time of separation of the cord (which on average was the eighth day). Nasal swabs were taken from the staff four times during the period of the experiment.

The total number of babies admitted to the nurseries during the course of the experiment was 82 to the masked nursery and 85 to the unmasked nursery.

The mean duration of stay in the masked nursery was just over 8½ days, the median being 9 days and the range

1 to 16 days. In the unmasked nursery the mean was 9 days, the median 10 days, and the range 2 to 16 days.

In the tables the bracketed increments are twice the standard errors of the percentage shown. Statistical significance is assessed on this basis.

Infection.—The infection rates in the two nurseries are shown in Table I. These are infections assessed clinically. All were minor infections. The infection rates in the two nurseries were practically the same. The sites of infection

TABLE I.—*Infection Rates*

Nursery	Total No. Admitted	Total Infected	Infection Rate
Masked	82	22	27% (±10)
Unmasked	85	27	30% (±10)

are shown in Table II. As between the masked and unmasked nurseries there is no statistical difference in the incidence of infection at the various sites.

TABLE II.—*Sites of Infection*

Nursery	Eye		Skin		Umbilicus	
	No.	%	No.	%	No.	%
Masked (22 infections)	13	59 (±21)	8	36 (±20)	1	5 (±9)
Unmasked (27 infections)	10	37 (±19)	16	59 (±19)	1	4 (±7)

Carriage.—The carriage rates for coagulase-positive staphylococci for the various sites on the infant and the staff nasal carriage rate are shown in Table III. There was no significant difference in the carriage rates for staphylococci on the eye, nose, or umbilicus in the two nurseries, and the total carriage rates were very similar. The staff nasal carriage rate was of the same order as the carriage rate on the babies.

TABLE III.—*Carriage*

	Nursery	No. Swabs	Staph. Coag. Pos.	Staph. Coag. Neg.	Others	No Growth	Staph. (Coag. Pos.) Carriage
Eye (4th day)	Masked	80	28	56	4	4	35% (±11)
	Unmasked	79	28	51	6	6	35% (±11)
Nose (8th day)	Masked	67	41	37	1	1	61% (±11)
	Unmasked	66	38	28	4	2	58% (±12)
Umbilicus (cord off)	Masked	62	44	18	27	3	71% (±11)
	Unmasked	65	36	16	36	6	55% (±12)
Total	Masked	209	113	111	32	8	54% (± 7)
	Unmasked	210	102	95	46	14	49% (± 7)
Nose	Staff	45	22	20	1	4	47% (±15)

Drug-sensitivity Patterns of Coagulase-positive Staphylococci Isolated

Each coagulase-positive staphylococcus isolated was subcultured and tested by the disk technique for sensitivity to six antibiotics and to sulphonamide. It was therefore possible to work out a drug-sensitivity pattern for the coagulase-positive staphylococci from the masked nursery, the unmasked nursery, and the staff.

These patterns, based on the resistance of the organism to the drugs specified, are shown in Table IV. Strains of coagulase-positive *Staphylococcus pyogenes* are classified as resistant to penicillin when their minimum inhibitory concentration exceeded 3 units per ml. and resistant to streptomycin, chloramphenicol, chlortetracycline, oxytetracycline, erythromycin, and sulphonamide when their minimum inhibitory concentration exceeded 1, 10, 2.5, 2.5, 2.5, and 100 μg./ml. respectively. All were found to be sensitive to erythromycin; thus this antibiotic is not included in the table.

TABLE IV.—*Drug Sensitivity Pattern*

Source	No. Staph.	Percentage of Strains Resistant to:					
		Sulph.	Penic.	Strep.	Chloram.	Chlortet.	Oxytet.
Masked	137	39 ± 8	75 ± 7	47 ± 9	14 ± 6	10 ± 5	18 ± 7
Staff	25	32 ± 19	44 ± 20	12 ± 12	8 ± 11	8 ± 11	8 ± 11
Unmasked	130	43 ± 9	75 ± 8	51 ± 9	8 ± 5	15 ± 6	15 ± 6

It can be seen that there is no significant difference in the drug sensitivity pattern of the staphylococci found in the babies in the masked and in the unmasked nurseries. If the patterns of the staphylococci found in these two groups of babies are compared with those of the staphylococci found on the nursing staff there is, however, a significant difference. This is seen in penicillin and streptomycin resistance. The highest penicillin and streptomycin resistance which the staff staphylococci could by chance have reached (using twice the standard error of the percentage) would have been 64% and 24% respectively. Both of these fall short of the lowest percentage resistance which could have occurred in the organisms from the masked and unmasked nurseries—namely 68% and 67% for penicillin and 38% and 42% for streptomycin.

Nursing Time Expended and Cost

Nursing Time.—The time expended on the various procedures involved in the masking and gowning regime was determined, using a stop-watch. These figures were applied to the whole 50-bedded unit and a schedule of nursing time expended was drawn up (Table V). At any one time the

TABLE V.—*Daily Nursing Time Expended on Masking and Gowning in a 50-Bedded (About 45 Babies) Maternity Unit*

Masking (Mask on and off=30 seconds)	
7 Nursing-staff change masks hourly	84 minutes
Processing of about 200 masks daily:	
Washing—20 minutes Cellophane inserts—50 minutes Autoclaving—40 minutes	110 ,,
1% loss of efficiency due to mask	101 ,,
	295 ,,
Gowning (Gown on and off=35 seconds)	
Gown changes—8/baby/day	210 minutes
Provision and disposal of 60 gowns per day	35 ,,
	245 ,,
Total nursing time	9 hours a day

average number of nurses looking after the babies was seven. As the average working day of a nurse is eight hours, more than the full daily working time of one nurse would be employed on masking and gowning.

Cost.—An attempt has been made to estimate the cost of masking and gowning in a maternity unit of this size (Table VI). Many factors are difficult to evaluate, and such

TABLE VI.—*Annual Cost*

	£
9 hours' nursing time a day	300
1,200 masks (each mask lasting 2 months)	65
120 gowns (each gown lasting 6 months)	165
Laundering, sterilizing, and repairing masks and gowns	100
	630

an estimation must be a very rough one. To the total cost, masking would contribute about £280 and gowning about £350.

Discussion

In this experiment we were concerned only with the effect of masking and gowning on the dissemination of staphylococci. The results would not necessarily be applicable to other bacteria or to viruses. From a quantitative point of view, however, there is no doubt that staphylococcal infection is the most important one affecting the newborn infant in maternity units.

The masking and gowning regime employed was as elaborate as is likely to be practicable in most maternity units. It was certainly more thorough than is practised in many. Yet our results show no difference in the rate of staphylococcal infection or in the staphylococcal carriage rate in the masked as compared with the unmasked nursery. At a time when the neonatal staphylococcal infection rate in the unit was high masking and gowning failed to exert any significant effect in reducing it.

Comparison of the drug-sensitivity patterns of the staphylococci found on the babies in the masked and unmasked nurseries and on the nursing staff probably gives a clue to the ineffectiveness of masking. In the unmasked nursery

there was nothing to stop the free dissemination of staphylococci from the nares and mouth of the nursing staff to the babies should such occur naturally; yet the pattern of staphylococci found on the babies differed from that found on the nurses. This suggests that little dissemination from mouth and nose of nurse to baby did in fact take place. The interposition of a mask between nurse and baby in the masked nursery would therefore not be expected to accomplish anything, and it did not. The same nursing staff did, of course, serve both nurseries. Were the predominant spread of infection to be—as we believe—from baby to baby indirectly, our results would be more easily understood.

Nurses in maternity units usually have a high nasal carriage rate for coagulase-positive staphylococci (Barber *et al.*, 1949; Rountree and Thomson, 1952; Edmunds *et al.*, 1955); it has been suggested that they may be an important source of infection of the infant (Allison and Hobbs, 1947). The drug-sensitivity pattern of staphylococci carried by such nurses may differ from or may resemble that found on the infants. Forfar *et al.* (1953) noted a difference in pattern, and suggested that nurses were not an important source of infection. Two years later, in the same maternity unit, staphylococci from nurses and babies showed a similar drug-sensitivity pattern and were predominantly of the same phage types (Forfar *et al.*, 1955). Edmunds *et al.* (1955) noted that the drug-sensitivity pattern from babies born at home was different from that of the domiciliary midwives attending them daily. Hutchison and Bowman (1957) noted that the drug-sensitivity pattern of babies' staphylococci differed from that of nurses and confirmed the difference by phage-typing. Edmunds *et al.* (1955) noted that the staphylococci carried by infants showed little resemblance to those found on their mothers, arguing against transmission from mother to baby. They suggested transmission from baby to mother as a more likely sequence of events. Hutchison and Bowman (1957) made similar observations, noting that when babies were nursed beside their mothers the mothers tended to pick up the staphylococci which the babies were carrying.

The fact that the babies' and nurses' staphylococci can be different suggests that nurses are not a constant or major source of babies' staphylococci, at least so far as transfer from the nose of the nurse is concerned. The fact that babies' and nurses' staphylococci may at times be similar should not be interpreted as evidence of transmission from nurse to infant. It would be surprising if not infrequently or even usually nurse and baby, dwelling in the same environment, did not pick up the same organisms and did not both have a high carriage rate. The frequent occurrence in both of a high carriage rate for the same type of staphylococci is much more likely to be a reflection of a common environment than an indication of direct transfer of organisms. The baby is probably the important source of infection from a quantitative point of view, but the nurse may act as the agent who introduces a particular staphylococcus into a maternity unit (Colbeck, 1949).

Our results can be related to the evidence regarding transmission of staphylococci from the mouth and nose in droplets. Hare and Thomas (1956) suggest that relatively few staphylococci are transferred direct by droplet spray. Duguid (1945) has shown that in normal breathing over a five-minute period no droplets or only a few may be produced. The investigations of Duguid (1946) and of Duguid and Wallace (1948) have shown that the few droplets originate in the nose rather than the mouth and only a small proportion of these will be infected with staphylococci even in a nasal carrier. From such investigations it would seem that breathing during 10 hours would at most infect the air with 100 or so *Staph. aureus* infected particles, about the same number as result from the liberation of dust from a carrier's clothing during 10 minutes' bodily movement or, as shown by Dumbell *et al.* (1948), from one use or flourish of an infected handkerchief. More droplets are released in coughing, loud talking, and sneezing than in breathing. Presumably such activities on the part of those nursing the newborn infants should be discouraged. Even sneezing, however, produces very few staphylococcal-infected droplets (Duguid and Wallace, 1948). The evidence obtained from experiments on *Staph. aureus* air infection in a maternity unit led Wallace and Duguid (1952) to conclude that air infection was not due in any important degree to droplet nuclei derived from nasal and mouth secretions.

In the light of these findings the unimportant role of the mask in controlling staphylococcal infection is not difficult to understand. It is even possible that a mask may have a negative effect; that the irritation of the face which it produces may encourage touching of a potentially contaminated area and contact infection via the hands. It is also possible that movement of the mask may rub off from the face particles contaminated with staphylococci.

The allocation of an individual gown to a baby is a practice which enjoys a considerable vogue as a prophylactic measure on the assumption that it will limit the transmission of infection which might occur with a communal gown. Yet the very act of putting on a gown at a baby's cot is likely to be a contaminating procedure. Dressing and undressing are activities which can result in heavy contamination of the atmosphere with bacteria-carrying particles, much more so than ordinary movement (Duguid and Wallace, 1948). Nasal carriers of *Staph. aureus* release into the air from their clothing on movement many times the number of bacteria which they release on sneezing (Duguid and Wallace, 1948). Once put on, a sterile gown of the usual surgical type only reduces the number of bacteria-carrying particles dislodged from the clothes on movement by half.

Nursing time is a valuable commodity, but it is usually a limited one. According to our calculations the time spent in carrying out a correct masking and gowning regime in the nurseries of a 50-bedded maternity unit is equivalent to more than the full-time service of a nurse. The nursing time spent on masking and gowning must be met at the expense of other calls on nursing time or, alternatively, an extra nurse must be employed. It must be decided whether among competing claims on nursing time masking and gowning are justifiable procedures or whether the additional cost of extra nursing personnel, etc., is the best way of spending limited funds.

It seems likely that in seeking prophylactic measures against staphylococcal infection in maternity units attention can be more profitably directed to the control of air-borne infection resulting from contamination of the atmosphere by dust from personal clothing, bedding, fomites, etc.; to the avoidance of contact with contaminated bedding, clothes, towels, hands, baths, etc. (Wallace and Duguid, 1952; Colbeck, 1956); and to the rendering non-infective of the baby infected with or carrying pathogenic staphylococci rather than to the masking and gowning of attendant personnel.

Summary

A controlled experiment was carried out in a maternity unit to determine the effectiveness of masking and gowning in reducing staphylococcal infection of and carriage on newborn infants. A strict masking and gowning regime was employed in one nursery (the "masked" nursery) but not in another (the "unmasked" nursery).

In both nurseries the same proportion of infants suffered from minor staphylococcal infections. The sites of occurrence of these infections were the eye and skin predominantly and also the umbilicus. Between the two nurseries there was no significant difference as to site of infection.

The carriage rate for staphylococci in the babies in the two nurseries was determined by examining swabs from the eye, nose, and umbilicus. The carriage rate for staphylococci in the attendant nursing personnel was determined by nasal swabbing. There was no significant difference in the carriage rates for babies in the masked and unmasked nurseries or between the babies and the attendant personnel.

There was no significant difference in the drug-sensitivity pattern of staphylococci isolated from babies in the two nurseries but a significant difference in pattern between babies' and nurses' staphylococci.

It is concluded that direct transfer of staphylococci from the nose and mouth of attendant personnel to the baby is not an important means of infection of the latter, and that masking and gowning in maternity nurseries is unlikely therefore to be an effective preventive measure.

An attempt has been made to assess the cost of masking and gowning in nursing time and money.

We wish to thank Sister Moore for the indispensable help she gave in this study, and Dr. J. P. Duguid for his helpful advice and criticism.

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FREEZE-DRIED B.C.G. VACCINE

RESULTS OF LABORATORY TESTS AND OF TRIALS AMONG SCHOOLCHILDREN IN MIDDLESEX

A PRELIMINARY REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR COMMITTEE ON THE STANDARDIZATION OF FREEZE-DRIED B.C.G. VACCINE *

In 1956 the first results were published of a controlled trial made to assess the efficacy in adolescents of the liquid B.C.G. vaccine prepared by the State Serum Institute, Copenhagen, Denmark (Medical Research Council, 1956). It was shown that the liquid vaccine was able to induce a high degree of tuberculin sensitivity and to confer, for at least two and a half years after administration, substantial protection against tuberculosis. This vaccine, which is extensively used in the United Kingdom in the vaccination of 13-year-old children and of those known to be in contact with tuberculosis, has certain disadvantages. Its keeping qualities are limited, and the State Serum Institute recommends that it should be used within 14 days of issue. This adds to the administrative difficulties of local health authority vaccination schemes and often results in waste of vaccine. A further disadvantage is that the liquid vaccine must be used before the results of laboratory tests for activity and safety can be known.

A freeze-dried B.C.G. vaccine has now been developed in England by Glaxo Laboratories Ltd., and its preparation has been described by Ungar, Farmer, and Muggleton (1956). It activity has been studied in infants by Lorber, Hart, Farmer, and Muggleton (1956), Griffiths and Gaisford (1956), and Lorber, Farmer, and Muggleton (1957). With the use of batches of this freeze-dried vaccine with appropriate viable counts tuberculin sensitivity was induced in a high proportion of infants; indeed, it proved as effective in this respect as the liquid vaccine. The dried and the liquid vaccines were also similar with respect to the production of local vaccination lesions and the incidence of local complications. As a result of these investigations the manufacturer decided to issue for clinical use a dried vaccine which, when reconstituted, had approximately 5 million viable particles per millilitre.

It is well known that the viable count of any B.C.G. vaccine may vary considerably with different batches; before the British dried vaccine could be used extensively it was regarded as essential to determine whether its viable count was as consistent from batch to batch as that of the Danish liquid vaccine. It was also thought desirable to carry out trials in 13-year-old schoolchildren—since the present local health authority vaccination scheme in this country applies to this age group—to compare the British dried vaccine with the Danish liquid vaccine as regards activity both in inducing tuberculin sensitivity and in producing local vaccination lesions. These trials were not designed to assess the value of the dried vaccine in the prevention of tuberculosis; this would have entailed a very prolonged and extensive investigation.

Laboratory Tests

Determination of Number of Viable Particles

The determination of the number of viable bacillary particles (viable count) in samples of both the dried and the liquid vaccine was made by the Medical Research Council's Biological Standards Control Laboratory, using one method throughout. For each batch the average count was obtained from the results of separate tests on six 1-ml. ampoules. The diluent used for reconstituting the dried vaccine and for making serial dilutions of both the dried and the liquid vaccine was Sauton medium to which 1/4,000 w/v Triton (WR. 1339) had been added to minimize aggregation. The initial suspension of the liquid vaccine was made by adding 1 ml. from each ampoule to 9 ml. of diluent and that of the dried vaccine by suspending the contents of one ampoule in 10 ml. of diluent. From these initial suspensions, serial dilutions were made and plated on nutrient medium, using a method similar to that described by Miles and Misra (1938). After investigating the suitability of a number of media it was decided to use oleic-acid–albumin–agar (Fenner, Martin, and Pierce, 1949). This medium was distributed in Petri dishes, which, after seeding, were kept in sealed "polythene" envelopes during the whole period of three to four weeks' incubation at 37° C. Tests were made with a number of batches of vaccine to determine the effect of including

Members of the Committee: Dr. D. G. Evans (chairman), Dr. E. T. Conybeare, Dr. A. J. Eley, Dr. P. D'Arcy Hart, Dr. D. A. Long, Dr. J. F. MacGregor, Dr. E. M. Madeley, Dr. C. Miller, Dr. T. M. Pollock, Dr. Ian Sutherland, Dr. D. Thomson, and Dr. T. W. Osborn (secretary).

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Field Work: Dr. R. G. Isaac, Dr. R. L. Lindon, and Dr. R. Prothero (Brentford, Chiswick, Heston, and Isleworth), Dr. A. V. Barrett, Dr. M. Watson, and Dr. A. Wheildon (Hendon), Dr. R. D. Gross, Dr. K. M. Hart, and Dr. S. R. Tangye (Ealing), Dr. R. Halperin and Dr. M. H. Snape (Wembley), Dr. L. Crawford, Dr. K. I. Kerr, and Dr. E. M. Waterhouse (Wood Green and Southgate), Dr. M. Heller (Acton), and Dr. N. Janes and Dr. C. Miller (Medical Research Council).

Co-ordination of Trials: Dr. C. Miller and Dr. T. M. Pollock assisted by Dr. N. Janes (Medical Research Council's Tuberculosis Research Unit).

Laboratory Tests: Dr. T. W. Osborn assisted by Miss K. South (Medical Research Council's Biological Standards Control Laboratory).

Analysis of Results: Miss B. J. Kinsley and Dr. Ian Sutherland (Medical Research Council's Statistical Research Unit).

Preparation of Report: Dr. T. W. Osborn, Dr. T. M. Pollock, and Dr. Ian Sutherland; Mrs. J. E. Hall (secretarial work).

5% of stored human blood in the above medium. It was found that the addition of blood to some lots of medium had no effect on the viable count, whilst with others a slightly higher count was obtained. It was decided, therefore, to incorporate blood in all subsequent lots of medium.

Freeze-dried B.C.G. Vaccine

Thirty-three production batches of this vaccine were tested by the Control Laboratory, and the viable counts for each individual batch are given in Fig. 1. In making the dried vaccine the manufacturer standardizes the total bacillary mass by opacity against a killed reference suspension before it is diluted to the desired concentration and freeze-dried. Of the batches examined, Nos. 114 to 129 were made from suspensions with half the opacity of Nos. 130 to 160. The

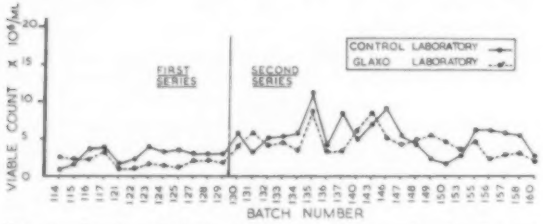

FIG. 1.—Results of viable count determinations by the Control Laboratory and Glaxo Laboratories of 33 batches of the dried vaccine.

viable counts of the first series ranged from 0.8 to 3.8 million per ml. and of the second series from 1.6 to 11.1 million per ml., the average counts of the two series being 2.7 and 5.3 million per ml. respectively.

Viable counts of all production batches are made by the manufacturer by a method already described (Ungar *et al.*, 1956), and only those batches with appropriate viable counts are issued. The manufacturer's results for the 33 batches tested by the Control Laboratory are also given in Fig. 1. The viable counts of the first series ranged from 1.0 to 3.5 million per ml., and of the second series from 2.2 to 8.7 million per ml., the average counts of the two series being 1.8 and 4.4 million per ml. respectively. It is evident, considering the large errors involved in viable count determinations, that there was a good correlation between the results from the two laboratories.

It was decided to use in the trials batches 116 and 117 from the first series and batches 131 and 133 from the second series. The results of the viable counts of these four batches, from both laboratories, are given in Table I. It will be seen that, despite the difference in initial opacity between the two batches from the first and the two from the second series, the determinations of viable count of all four batches were similar.

TABLE I.—*Results of Determinations of Viable Counts of the Batches of B.C.G. Vaccine Used in the Trials*

Vaccine	Batch No.	Viable Count in Millions/ml.	
		Results of Control Laboratory	Results of Glaxo Laboratories
Dried	116	3·6	2·2
	117	3·7	3·5
	131	3·2	5·7
	133	5·2	4·5
		Results of State Serum Institute	
Liquid	1240	17·7	
	1241	18·9	
	1242	9·0	
	1243	12·3	
	1244	9·6	
	1245	10·5	
	1247	11·7	
	1248	14·1	
	1249	16·3	
	1250	12·9	
	1251	12·0	
	1257	14·8	
	1258	22·5	
	1259	15·1	
	1260	16·6	

Liquid B.C.G. Vaccine

The determinations of the viable count of this vaccine were made by the State Serum Institute, Copenhagen. The results obtained with a series of 21 batches, including the 15 used in the trials, are given in Fig. 2; the counts ranged from 9.0 to 22.5 million per ml. The values for the 15 batches used in the trials are also shown in Table I.

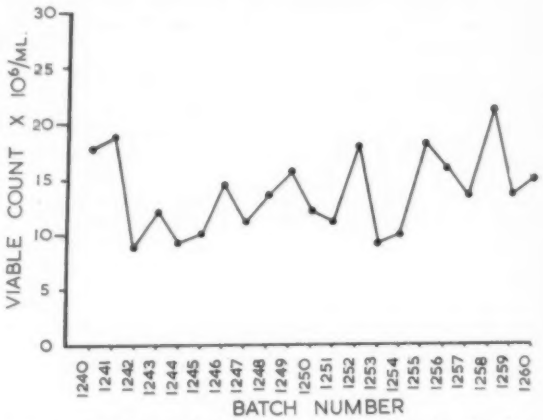

FIG. 2.—Results of viable count determinations by the State Serum Institute of 21 batches of the liquid vaccine.

Comparison of Dried and Liquid Vaccine

Viable counts of 13 batches of the liquid vaccine, including 5 of the 15 used in the trials, were also made by the Control Laboratory, and values were obtained of the same order as those of the State Serum Institute. These 13 batches were tested in parallel with 13 batches of the dried vaccine, including the four used in the trials, employing, as a reference in each test, batch No. 125 of the dried vaccine. Six ampoules were used for the determination of the viable count of each batch under test and two ampoules for each determination of the reference batch. The results of this series of tests are shown in Fig. 3. The two vaccines are manufactured by fundamentally different processes producing dissimilar bacillary aggregates. No valid comparison can therefore be made of the viable counts of the dried with those of the liquid vaccine. It is justifiable, however, since the viable counts for the reference batch were similar over the whole series of tests, to compare the *variation* in the counts of the batches of dried vaccine with that of the

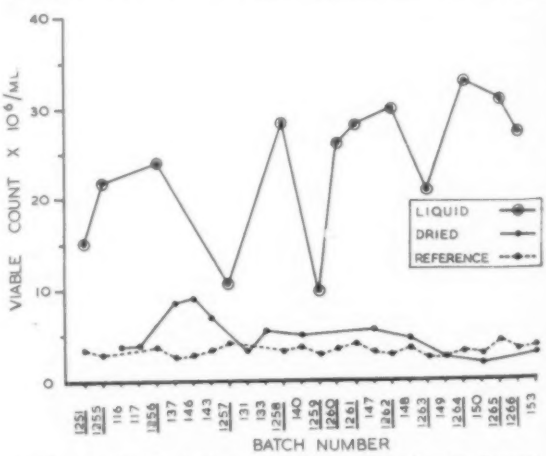

FIG. 3.—Results of viable count determinations by the Control Laboratory of 13 batches of the liquid vaccine, 13 batches of the dried vaccine, and one batch of dried vaccine, No. 125, as reference. The batches were tested in the order shown; the numbers of the batches of liquid vaccine are underlined.

batches of liquid vaccine. Fig. 3 shows that there was a similar range of variation from batch to batch with each type of vaccine; with the batches of liquid vaccine the viable counts ranged from 9.8 to 32.9 and with those of the dried vaccine from 1.6 to 9.0 million per ml.

Trials in Schoolchildren

General Plan

The trials were made in six areas in Middlesex. Between January and July, 1957, tuberculin tests were done on 6,405 children aged 13 and 14 years, and those who were tuberculin-negative were divided by an effectively random process into two groups of similar size. One group was vaccinated with the British dried vaccine and the other with the Danish liquid vaccine. The vaccination sites were examined and tuberculin tests were repeated after 5 to 7 weeks or after 10 to 17 weeks. The investigations were co-ordinated centrally and the procedures standardized throughout. It is planned to make a further examination one year after vaccination.

The batches of the liquid vaccine were drawn from the normal supply of 1-ml. ampoules received each week from Copenhagen for distribution to local health authorities; in all, 15 batches were used in the trials, each within 11 days of issue. Four batches of the dried vaccine issued in 1-ml. ampoules were used, each from 5 to 10 months after preparation. Both the liquid and dried vaccines were stored in a refrigerator. The numbers of all the batches of vaccine used in the trials and their respective viable counts are given in Table I.

In testing the tuberculin sensitivity of children both before and after vaccination, the same batch of old tuberculin, the same dilutions, and the same criteria of positivity were used as in the current Medical Research Council tuberculosis vaccines clinical trial.

Tuberculin Sensitivity before Vaccination

Each child was given the following standard examination. An intracutaneous tuberculin (Mantoux) test was made on the left forearm with 3 tuberculin units (T.U.), using 0.1 ml. of 1/3,000 old tuberculin (international standard strength), and after 72 hours the greatest diameter of palpable induration was recorded. If there was no induration, or if its diameter was less than 5 mm., the reaction to 3 T.U. was regarded as negative and a second intracutaneous test was made on the same forearm with 100 T.U., using 0.1 ml. of 1/100 old tuberculin. The greatest diameter of induration in this second test was also recorded after 72 hours, and children with no induration or an induration of less than 5 mm. diameter were regarded as negative reactors to 100 T.U. and so were eligible for vaccination.

A total of 6,406 children completed the initial tuberculin tests; of these, 544 (8.5%) gave positive reactions to 3 T.U., and a further 1,536 (24.0%) reacted to 100 T.U. A total of 4,326 children (67.5%) were thus negative to 100 T.U.

Vaccination of Children

The tuberculin-negative children born in January, March, May, July, September, or November were given the liquid vaccine and those born in the alternating months were given the dried vaccine. The dried vaccine was reconstituted by adding 1 ml. of sterile distilled water to each ampoule, drawing the suspension into a syringe and expelling it into the ampoule at least six times. The dose of both the dried and liquid vaccines was 0.1 ml. given intracutaneously into the lower deltoid area of the left arm on the day the result of the tuberculin test to 100 T.U. was recorded.

Of the 4,326 tuberculin-negative children, 4,293 were correctly vaccinated, 2,242 receiving the liquid and 2,051 the dried vaccine. The remaining 33 children either were not given the appropriate vaccine or refused vaccination and were excluded from the analysis.

Tuberculin Sensitivity after Vaccination

The vaccinated children in some areas were re-examined between 5 and 7 weeks (nearly all at 6 weeks) after vaccination and in the others between 10 and 17 weeks (nearly all between 11 and 14 weeks) after vaccination. As in the first examination, the children were tested with 3 T.U. and those who were negative to this dose were given a second dose of 100 T.U.

Of the 4,293 vaccinated children, 1,620 were chosen for tuberculin-testing at 5 to 7 weeks and 1,467 (90.6%) completed the tests. Of these, 780 had been vaccinated with the liquid vaccine and 687 with the dried. A similar proportion of those given the liquid and the dried vaccine failed to complete the tests. The results of the tuberculin tests at 5 to 7 weeks for each of the four batches of dried and for the batches of liquid vaccine used concurrently are shown in Table II. For all batches combined, 97.1% of those given the liquid were positive to 3 T.U. compared with 90.5% of those given the dried; this difference is significant at the 1% level. When each of the four batches of dried vaccine is individually compared with the corresponding batches of liquid vaccine, it is seen that the conversion rates to 3 T.U. for those children given the liquid ranged from 93.9% to 100% and for those given the dried vaccine from 83.0% to 100%. However, in both the liquid and the dried vaccine groups, all those children negative to 3 T.U. reacted to 100 T.U.

Table II also shows the degree of tuberculin sensitivity as measured by the diameter of induration produced by 3 T.U. at 5 to 7 weeks. For all batches combined, the mean diameter of the positive reactions was 11.9 mm. for those children given the liquid vaccine and 10.5 mm. for those given the dried; this difference is significant at the 1% level. A similar difference was found on comparing each batch of dried with the batches of liquid vaccine used concurrently. Fig. 4 gives the distribution of the size of the reactions to 3 T.U.; it is seen that with both types of vaccine the range was similar.

The remaining 2,673 of the 4,293 vaccinated children were due for tuberculin-testing at 10 to 17 weeks after vaccination, and 2,234 (83.6%) completed the tests. Of these, 1,149 had been vaccinated with the liquid vaccine and 1,085 with the dried. A similar proportion of those given the liquid and the dried vaccine failed to complete the tests. The results of the tuberculin tests at 10 to 17 weeks are shown in Table III for each of the four batches of dried and for the corresponding batches of liquid vaccine. For all batches together, 95.5% of the children given the liquid were positive to 3 T.U. compared with 90.3% of those given the dried

TABLE II.—*Results of Tuberculin Tests in Children 5 to 7 Weeks After Vaccination with the Dried and the Liquid Vaccine*

Period in Use	Liquid Vaccine						Dried Vaccine					
	Batch No.	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U. Positive to 100 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)	Batch No.	No. of Children Completing Tests	Positive to 3 T.U.		Negative to 3 T.U. Positive to 100 T.U.		Mean Diameter of Positive Reactions to 3 T.U. (mm.)
			No.	%	No.	%				No.	%	No.	%	
28/1/57 to 2/2/57 ..	1241	43	42	97·7	1	2·3	12·4	116	45	39	86·7	6	13·3	9·9
3/2/57 to 16/2/57 ..	1242, 1243	179	168	93·9	11	6·1	10·5	117	159	132	83·0	27	17·0	9·2
18/2/57 to 27/3/57 ..	1244, 1247	98	98	100·0	0	0	11·4	131	86	86	100·0	0	0	10·1
28/3/57 to 6/6/57 ..	1250/55, 1257/60	460	449	97·6	11	2·4	12·4	133	397	365	91·9	32	8·1	11·0
All batches	.. .. ..	780	757	97·1	23	2·9	11·9	All batches	687	622	90·5	65	9·5	10·5

vaccine ; this difference is significant at the 1% level. When each of the four batches of dried vaccine is individually compared with the corresponding batches of liquid vaccine, it is seen that the conversion rates to 3 T.U. for those children given the liquid vaccine ranged from 91.4% to 98.9% and for those given the dried from 86.0% to 95.2%. Nevertheless, all those children in both the liquid and the dried vaccine groups who were negative to 3 T.U. reacted to 100 T.U.

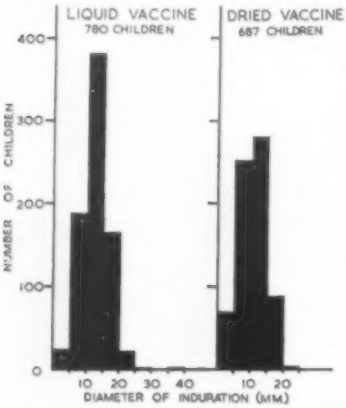

FIG. 4.—Diameter of induration to 3 T.U. in children 5 to 7 weeks after vaccination.

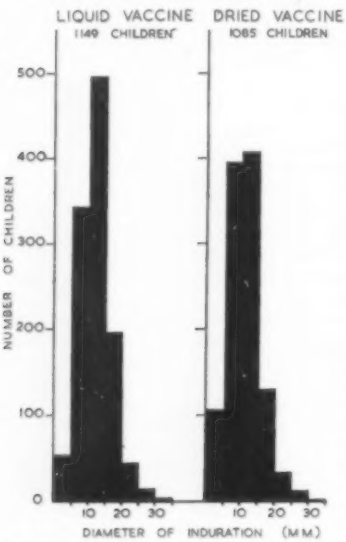

FIG. 5.—Diameter of induration to 3 T.U. in children 10 to 17 weeks after vaccination.

Table III also shows the degree of tuberculin sensitivity as measured by the diameter of induration produced by 3 T.U. at 10 to 17 weeks. For all batches together, the mean diameters of the positive reactions were 11.7 and 10.9 mm. for those children given the liquid and the dried vaccine respectively. Again it is evident that a slightly greater degree of sensitivity was induced by the liquid than by the dried vaccine ; this difference is significant at the 1% level. A similar difference was found when each batch of the dried was compared with the batches of liquid vaccine used concurrently. Fig. 5 gives the distribution of the size of the reactions to 3 T.U. ; as with the children tested after 5 to 7 weeks, the range was similar with both types of vaccine.

Local Vaccination Lesions

On the day the vaccinated children were re-tested with tuberculin, the local vaccination lesions were examined and their diameters recorded. The number of children whose vaccination lesions were examined was somewhat larger than the number who completed the tuberculin test. Local lesions were observed in all children examined, both in the liquid and in the dried vaccine groups. The mean diameters of the lesions examined 5 to 7 weeks after vaccination were 9.6 mm. in 811 children receiving the liquid and 8.4 mm. in 725 receiving the dried vaccine (Fig. 6), this difference being significant at the 1% level. A smaller non-significant difference was evident when the lesions were examined 10 to 17 weeks after vaccination, the mean diameter being 8.2 mm. in 1,229 receiving the liquid and 7.9 mm. in 1,159 receiving the dried vaccine (Fig. 7). Small differences were also apparent when comparing the lesions produced by each batch of dried with the batches of liquid vaccine used concurrently. As may be seen from Figs. 6 and

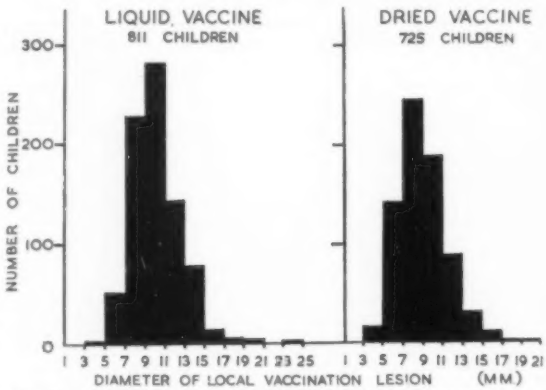

FIG. 6.—Diameter of local vaccination lesions in children 5 to 7 weeks after vaccination.

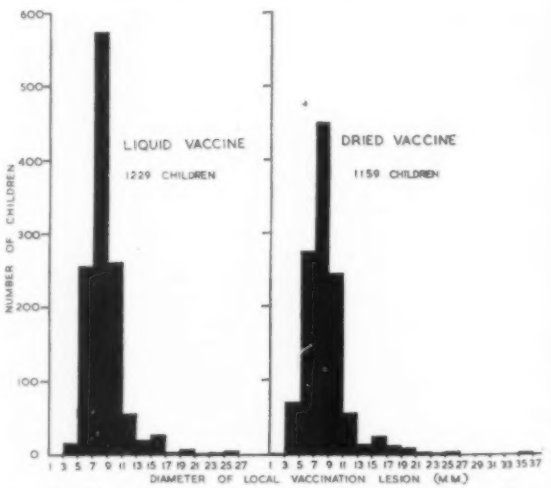

FIG. 7.—Diameter of local vaccination lesions in children 10 to 17 weeks after vaccination.

TABLE III.—*Results of Tuberculin Tests in Children 10 to 17 Weeks After Vaccination with the Dried and the Liquid Vaccine*

Period in Use	Liquid Vaccine: Batch No.	No. of Children Completing Tests	Positive to 3 T.U. No.	Positive to 3 T.U. %	Negative to 3 T.U. Positive to 100 T.U. No.	Negative to 3 T.U. Positive to 100 T.U. %	Mean Diameter of Positive Reactions to 3 T.U.(mm.)	Dried Vaccine: Batch No.	No. of Children Completing Tests	Positive to 3 T.U. No.	Positive to 3 T.U. %	Negative to 3 T.U. Positive to 100 T.U. No.	Negative to 3 T.U. Positive to 100 T.U. %	Mean Diameter of Positive Reactions to 3 T.U.(mm.)
21.1.57 to 2.2.57 ..	1240, 1241	217	212	97·7	5	2·3	11·5	116	171	147	86·0	24	14·0	10·1
3.2.57 to 16.2.57 ..	1242, 1243	213	207	97·2	6	2·8	11·6	117	191	180	94·2	11	5·8	10·6
18.2.57 to 24.3.57 ..	1244/5, 1247/9	444	406	91·4	38	8·6	11·7	131	492	433	88·0	59	12·0	10·9
25.3.57 to 8.4.57 ..	1249, 1251	275	272	98·9	3	1·1	11·9	133	231	220	95·2	11	4·8	11·5
All batches	.. .. ..	1,149	1,097	95·5	52	4·5	11·7	All batches	1,985	980	90·3	105	9·7	10·9

7, the diameters of the majority of the lesions produced by both types of vaccine lay between 5 and 15 mm. There were no complications as a result of vaccination with either vaccine.

Tuberculin Sensitivity and Vaccination Lesions in Relation to Vaccine Used

As mentioned previously, the dried vaccine batches 116 and 117 had an initial optical density half that of batches 131 and 133. In Table IV the results with batches 116 and 117 and with 131 and 133 are compared with those of the batches of liquid vaccine used concurrently. The comparison is based on three criteria—namely, the percentage of children who gave positive reactions to 3 T.U., the mean diameter of positive reactions to this test, and the mean diameter of the local vaccination lesions. It is evident that in each comparison the value for each of the criteria was slightly greater for the liquid than for the dried vaccine. The differences between the liquid and the dried vaccine were greater in the tests with batches 116 and 117 than in those with 131 and 133. This is probably related to the fact that the former two batches had a lower initial optical density.

TABLE IV.—*Results of Tuberculin Tests and Examination of Local Vaccination Lesions in Children after Vaccination with (a) the Dried Vaccine Batches 116 and 117; (b) the Dried Vaccine Batches 131 and 133; and (c) the Corresponding Batches of Liquid Vaccine*

Weeks after Vaccination	Dried Vaccine Batches	No. of Children Completing Skin Tests		Percentage of Children Positive to 3 T.U.			Mean Diameter of Positive Reactions to 3 T.U. (mm.)			Mean Diameter of Vaccination Lesions (mm.)		
		Liquid Vaccine	Dried Vaccine	Liquid Vaccine	Dried Vaccine	Difference	Liquid Vaccine	Dried Vaccine	Difference	Liquid Vaccine	Dried Vaccine	Difference
5 to 7	116, 117	222	204	94·6	83·8	+10·8	10·92	9·38	+1·54	9·55	7·41	+2·14
	131, 133	558	483	98·0	93·4	+4·6	12·25	10·86	+1·39	9·68	8·77	+0·91
10 to 17	116, 117	430	362	97·4	90·3	+7·1	11·57	10·39	+1·18	7·50	6·72	+0·78
	131, 133	719	723	94·3	90·3	+4·0	11·80	11·10	+0·70	8·57	8·48	+0·09

An analysis was made of the tuberculin sensitivity and vaccination reactions produced by each individual batch of vaccine. The results did not suggest, either with the four batches of dried or with the 15 batches of liquid vaccine, that there was any correlation between the activity of the different batches in children and their viable counts, but the numbers of children given each batch were relatively small.

Summary and Conclusions

Viable counts were made by both the Biological Standards Control Laboratory and the manufacturer of a number of batches of British freeze-dried B.C.G. vaccine prepared over a period of twelve months. It was shown that the range of variation in viable count from batch to batch was no greater with this vaccine than it was with a number of batches of Danish liquid B.C.G. vaccine which were similarly tested.

The activity of the dried vaccine was compared with that of the liquid vaccine in strictly controlled trials among approximately 4,000 tuberculin-negative schoolchildren aged 13 and 14 years in six areas in Middlesex. These children were vaccinated with either the dried or the liquid vaccine, the selection being made by an effectively random process. Four batches of the dried vaccine and 15 batches of the liquid vaccine were used.

Tests of tuberculin sensitivity and examination of local vaccination lesions were made in some areas 5 to 7 weeks and in others 10 to 17 weeks after vaccination. The overall conversion rates to 3 tuberculin units (T.U.) at 5 to 7 weeks were 90.5% for those children given the dried and 97.1% for those given the liquid vaccine; the corresponding figures for tests made at 10 to 17 weeks were 90.3% and 95.5% respectively. All children who were negative to 3 T.U. either at 5 to 7 weeks or at 10 to 17 weeks subsequently gave positive reactions to 100 T.U. The vaccination lesions produced by the dried vaccine were slightly smaller than those produced by the liquid vaccine. No complications as a result of vaccination were recorded with either type of vaccine.

In preparing the dried vaccine the manufacturer standardizes the total bacillary mass by optical density before it is freeze-dried. Of the four batches tested in children, the two batches which had an initial optical density twice that of the other two proved to be slightly the more active, as judged by the tuberculin sensitivity produced and the size of the vaccination reactions.

The conversion rates produced by the batches of dried vaccine, although slightly less than those produced by the liquid, can be relied upon to give a high degree of protection against tuberculosis, since in a previous trial of the liquid vaccine (Medical Research Council, 1956) a conversion rate to 3 T.U. of 86% was shown to do so.

The dried vaccine was given in several areas and by different physicians under conditions similar to those of the current vaccination schemes in this country for 13-year-old schoolchildren. The results are thus likely to resemble those which would be obtained if batches of dried vaccine with viable counts similar to those used in the trials were used on a large scale for adolescent schoolchildren.

The results so far reported apply to tests made up to three months after vaccination. A further comparison of the liquid and the dried vaccines is to be made by testing the tuberculin sensitivity one year after vaccination.

The batches of dried vaccine were stored in the refrigerator for 5 to 10 months before being used in children, and such periods of storage did not appear to affect the ability of the vaccine to produce a satisfactory tuberculin sensitivity. Further examinations are to be made of the keeping qualities of the vaccine at room temperature. Until the results of these tests are known it is considered that the dried vaccine should be kept in a refrigerator until used.

The Medical Research Council's Committee on the Standardization of Freeze-dried B.C.G. Vaccine wishes to thank Dr. J. Ungar and his colleagues, of Glaxo Laboratories Ltd., and Dr. K. Tolderlund and his colleagues, of the State Serum Institute, Copenhagen, for their co-operation in this investigation. Thanks are also due to Glaxo Laboratories Ltd. for the supply of freeze-dried B.C.G. vaccine.

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ANTITHYROID ACTIVITY OF N-PHTHALYL GLUTAMIC ACID IMIDE (K 17)

BY

J. McC. MURDOCH, F.R.F.P.S., M.R.C.P.Ed.
Senior Registrar

AND

G. D. CAMPBELL, M.B., M.R.C.P.Ed.
Research Fellow

From the Department of Therapeutics, University of Edinburgh, and the Royal Infirmary, Edinburgh

N-phthalyl glutamic acid imide (K 17) was first synthesized in Germany by Kunz *et al.* (1956) while seeking to produce a drug combining the advantages of the barbiturates without their undesirable side-effects. This tasteless white crystalline substance is an imide of glutamic acid and a derivative of piperidine. It is reported to have a "calming psychological effect" and has been used extensively on the Continent in doses of 25 to 50 mg. two to four times daily, when it acts as a daytime sedative, while in doses of 50 to 100 mg. it acts as a night-time hypnotic (Esser and Heinzler, 1956; Jung, 1956). A toxic dose of this substance in experimental animals could not be ascertained (Kunz *et al.*, 1956): this is not only due to the fact that the compound is sparingly soluble in water, but also because of its extremely low toxicity. No side-effects were observed following the administration of K 17 to mice, rats, guinea-pigs, and rabbits (Kunz *et al.*, 1956).

In Germany clinical experience has already led to the suggestion that the drug is virtually non-toxic and will prove valuable in various psychological disturbances such as anxiety states, mild depression, excitability, and some vegetative dystonias (Esser and Heinzler, 1956; Jung, 1956; Stärk, 1956). These workers observed marked reduction of the raised basal metabolic rate in mild and moderately severe cases of hyperthyroidism as the result of K 17 therapy. No published work has so far established whether these effects are brought about by a direct action on the thyroid gland or by causing a general reduction in metabolism in some other way.

The antithyroid action of K 17 was therefore assayed by the method of Stanley and Astwood (1947) in order to determine whether the effects on the human basal metabolic rate, mentioned above, were in fact related to depression of thyroid function.

Method

In euthyroid patients, if thyroid activity—measured by standard counting techniques—after a tracer dose of ^{131}I is plotted against the square root of the time in minutes, the resultant curve is seen to be a straight line persisting for up to 10 hours after the administered dose: drugs exhibiting antithyroid effect can cause deviations from this straight line, and are grouped by Stanley and Astwood into the following grades: 0, no effect; 1, questionable or slight effect; 2, partial suppression of uptake; 3, complete inhibition for less than 4 hours; 4, complete inhibition for more than 4 to 24 hours; and 5, complete inhibition for more than 24 hours.

The effects on the accumulation gradient in the thyroid gland of varying doses of K 17 were studied in nine adult euthyroid patients, following tracer doses of 20 μC of ^{131}I.

Results

The drug was administered in doses varying from 50 to 400 mg., and the effects are shown in the accompanying Table and in three cases are represented graphically (Figs. 1–3).

Effects of N-phthalyl Glutamic Acid Imide on Thyroid Uptake

Case No.	Dosage (mg.)	Effect	"Grade" (Stanley and Astwood, 1947)
1	50	No effect	0
2	100	Partial suppression of uptake	2
3	150	Effect questionable or slight	1
4	150	Slight partial suppression	2
5	200	" " "	2
6	200	Effect questionable or slight	1
7	200	Slight partial suppression	2
8	200	Complete suppression for less than 4 hours	3
9	400	" " " " "	3

In Case 1 no effect was observed after a 50-mg. dose (Fig. 1); in Cases 3 and 6, given doses of 150 and 200 mg. respectively, the effects were questionable or slight; in Cases 2, 4, 5, and 7, after doses of 100, 150, 200, and 200 mg. respectively, there was obvious partial suppression of uptake (Fig. 2, Case 2). After 200-mg. and 400-mg. doses in Cases 8 and 9 (Fig. 3) complete inhibition was obtained, followed by release between 75 and 120 minutes later.

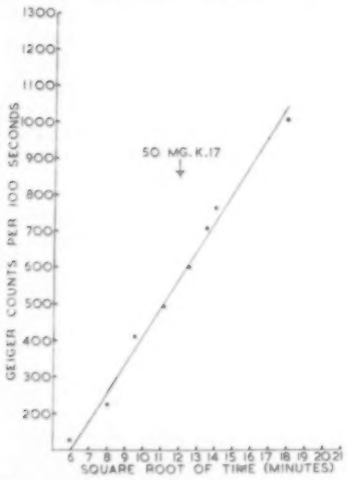

FIG. 1.—Case 1. Effect of 50 mg. K 17 on accumulation gradient of thyroid gland.

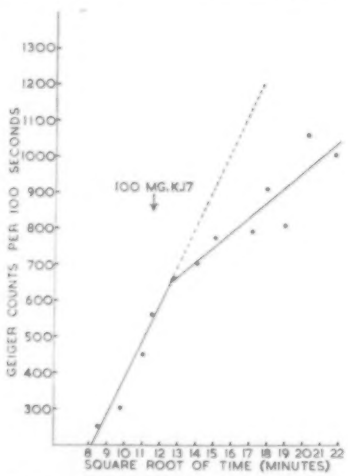

FIG. 2.—Case 2. Effect of 100 mg. K 17 on accumulation gradient of thyroid gland.

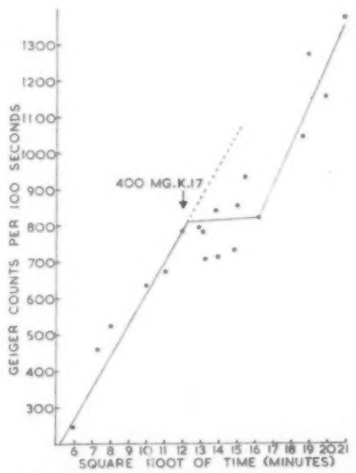

FIG. 3.—Case 9. Effect of 400 mg. K 17 on accumulation gradient of thyroid gland.

Side-effects.—In doses of 200 mg. or more the drug caused drowsiness and a tendency to sleep in five patients. The sleep so induced was apparently deep, but a slight stimulus produced an immediate awakening without obvious mental "cloudiness." In fact, one patient, when awakened, denied ever having been asleep at all. Complaints of excessive thirst and hunger may have been related to the comparatively lower intake of food and fluid necessitated by the technique of the test. There were no complaints of "hangover" or drowsiness on the morning after the test.

Summary and Conclusion

The effects of N-phthalyl glutamic acid imide (K 17) on thyroid uptake of radioactive iodine have been assessed in nine euthyroid patients.

From the results obtained it appears that N-phthalyl glutamic acid imide has a mild but definite antithyroid activity when given in doses of 200 mg. or more. At present the mode of its action is unknown. In the meantime, therefore, it would seem unjustifiable to use the drug for long-term sedative or hypnotic therapy, pending the results of a more detailed study of its long-term effects in a larger series of patients, and notably those suffering from mild or moderately severe hyperthyroidism.

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THE ENANTHEM OF GLANDULAR FEVER

BY

F. I. CAIRD, M.R.C.P.

Late Captain, R.A.M.C.; General Hospital, Birmingham

AND

P. R. HOLT, M.B., B.S.

Late Captain, R.A.M.C.; St. Luke's Hospital, New York

The manifestations of glandular fever are well known to be very varied, and the diagnosis is usually made only after laboratory investigation. Any clinical aid to diagnosis is therefore of value.

Many major reviews of the disease do not mention the occurrence of an enanthem (Tidy, 1934; Contratto, 1944; Press *et al.*, 1945; Gardner and Paul, 1946; Tidy, 1950; Stevens *et al.*, 1951). However, Downey and McKinlay (1923), in their classical paper describing the characteristic atypical monocyte, state that two of their nine cases had haemorrhagic lesions on the palate. Glanzmann (1930) described papular and petechial lesions on the palate in glandular fever and discussed their differential diagnosis with respect to acute leukaemia and thrombocytopenic purpura. Kilham and Steigman (1942) described petechiae in the mouth of 8 of their 20 cases. One other patient had irregular red papules on the palate. Milne (1945), Read and Helwig (1945), Wechsler *et al.* (1946), and Müller (1950) noted petechiae in the oral cavity in a few of their cases.

Berberich and Thomas (1949) and Hoagland (1952) drew attention to the diagnostic value of palatal lesions. They described groups of petechiae on the hard and soft palate, 5 to 20 in number. Bender (1954), Holzel (1954), and Shiver *et al.* (1956) independently gave more detailed descriptions of the enanthem. It consists of 10 to 100 small petechiae, usually at the junction of the hard and the soft palate, appearing from the third to the seventh day and disappearing after three to four days. They stress the absence of cutaneous purpura and the normal platelet count in those cases investigated.

Leibowitz (1953) described another lesion in 4 of his 25 cases: an irregular white macule about 2 mm. in diameter, surrounded by an erythematous base, persisting 24 hours or so, and occurring on the soft palate, tonsillar pillars, and tonsils.

The purpose of this communication is to confirm the diagnostic value of the enanthem and to discuss other similar lesions.

Material and Methods

At least 200 patients with acute febrile illnesses, with lymphadenopathy, or with jaundice, in whom glandular fever was a diagnostic possibility, were seen in five military hospitals between September, 1955, and May, 1957. Nearly all were males in the Service age group, but a few were females and children. Of 51 who had palatal lesions, 45 had at least one blood film examined and one Paul–Bunnell test performed. Four of the remaining six were young children, and are excluded from further consideration. The criteria used for the diagnosis of atypical mononuclear cells approximate to those of Downey and McKinlay (1923), although exact classification was not attempted.

The Paul–Bunnell reaction was not considered positive unless a titre of 1 in 80 or more was found after absorption with guinea-pig kidney and no significant titre after absorption with ox cells, according to the technique of Davidsohn (1937). Heterophil antibodies of this titre and pattern are generally regarded as occurring only in glandular fever (Leibowitz, 1953).

Results

The 45 patients investigated can be divided into four groups (see Table).

	Group A	Group B	Group C	Group D	Total
Glandular fever	Proved	Proved	Possible	No evidence	—
Atypical mononuclear cells	Seen	Not seen	Seen	Not seen	—
Paul–Bunnell test	Pos.	Pos.	Neg.	Neg.	—
Total No. of cases	23	5	7	10	45
Petechiae alone. More than 5	12	2	1	3	18
,, ,, Less than 5	6	3	4	2	15
Red macules. Alone	—	—	—	2	2
,, ,, With petechiae	3	—	—	1	4
Linear macules. Alone	—	—	1	—	1
,, ,, With petechiae	1	—	—	—	1
,, ,, With red macules	—	—	—	1	1
White macules (with petechiae)	1	—	1	—	2
Vesicles (with petechiae)	—	—	—	1	1

Two patients not investigated had vesicular lesions alone.

Group A comprised 23 patients with positive haematological and serological evidence of glandular fever as defined.

Group B consisted of five patients serologically positive but without atypical mononuclear cells. Two had only one blood film examined, on the second and fourth days. The blood in these two cases may well have been examined too early, for by the eighth day Stevens *et al.* (1952) found that only 50% of 210 cases had developed atypical cells. In view of the diagnostic significance of the differential Paul–

Bunnell reaction in the titre used, these five patients are considered with the 23 in group A as having "proved glandular fever."

Group C comprised seven patients in whom atypical mononuclear cells were found but the serology was negative. In two cases the titre in the Paul–Bunnell test rose between the first and second tests. In two more no Paul–Bunnell test was carried out after the 11th day. At this stage of the illness the test is often negative (Gardner and Paul, 1946). Further, a varying proportion of cases in different series have persistently negative Paul–Bunnell reactions. Thus, despite the known frequent occurrence of atypical mononuclear cells in other conditions (Shubert *et al.*, 1954), these patients are considered to have "possible glandular fever."

Group D consisted of 10 patients in whom there was neither haematological nor serological evidence of glandular fever. Only three had the blood examined after the ninth day. These patients are considered as having "no evidence of glandular fever."

Types of Palatal Lesion

Five types of lesion were seen:

1. *Petechiae.*—These are 1–2 mm. across, irregular in outline, and purple in colour. They usually occur at the junction of the soft and the hard palate, but may be seen anywhere on the palate. They may number from 1 to 50 or so. If infrequent they tend to be smaller, angular in shape, and somewhat redder. If numerous they may coalesce, but there are always a few small and clearly petechial lesions to indicate the nature of the eruption. Neither the symmetrical distribution nor the crescentic grouping described by Holzel (1954) is often seen. The petechiae first appeared 30 hours after the first symptom, but often developed on the third day. Each lesion lasted three to four days. Several crops may occur. In one case they were seen as late as the 26th day of illness. Petechiae occurred in all clinical varieties of glandular fever and bore no relation to the type of sore throat observed, the height of fever, the degree of adenopathy, or the presence of splenomegaly or exanthem. In most cases they disappeared within 48 hours of the fever settling. A second crop was occasionally associated with a second rise in temperature. Eighteen patients had more than five petechiae and no other palatal lesions: 14 had proved and 1 had possible glandular fever; three had undoubted rubella. Fifteen had fewer than 5 petechiae and no other lesions: of these, 9 had proved and 4 possible glandular fever, and 2 no evidence of it. Two patients, both with proved glandular fever, had petechiae on the buccal mucosa; one of these developed transient skin purpura and microscopic haematuria, but no thrombocytopenia.

2. *Red Macules.*—These are 3–4 mm. across, roughly circular, and deep red in colour. They occur anywhere on the palate, number up to three, and were seen from the 1st to the 14th day of illness. Two patients had these lesions alone: neither had evidence of glandular fever. Four had red macules and petechiae; three of them had proved glandular fever and one no evidence of it.

3. *Linear Macules.*—These are pinkish macular lesions 1 mm. across and 6–8 mm. long on the soft palate, sometimes arranged in a radial fashion; they were seen in three cases from the 7th to the 18th day of illness. Two had no evidence of glandular fever (one with these lesions alone and one with linear and red macules), while one patient with linear macules and petechiae had proved glandular fever.

4. *White Macules.*—Two patients had the lesion described by Leibowitz (1953); both had petechiae—one had possible and one proved glandular fever.

5. *Vesicular Lesions.*—Obviously vesicular lesions with erythematous surround were seen in three patients. One had a transient urticaria of unknown cause, another chickenpox: neither had blood examinations. The third had petechiae around the palatal vesicles and no evidence of glandular fever; the clinical picture was that of herpangina (Zahorsky, 1924; Huebner *et al.*, 1951), but virological studies were not carried out.

Discussion

These results confirm the findings of Berberich and Thomas (1949) and subsequent authors concerning the positive value of multiple palatal petechiae in the clinical diagnosis of glandular fever. If fewer than five petechiae are present there is still a strong suspicion of the disease.

Haemorrhagic lesions in the palate are not, of course, confined to glandular fever. They may occur in leukaemia (Love, 1936) and in purpuric diseases, but in such conditions petechiae on the buccal mucosa, other lesions in the mouth, and cutaneous petechiae or purpura should be present (Glanzmann, 1930). They are described in meningococcal meningitis, in the exanthematic rickettsial illnesses, and in dengue (Stewart, 1944), but only as part of a profuse and usually diagnostic exanthem.

The enanthem of scarlet fever (Wiener, 1947), measles (Koplik, 1896; Wiener, 1947), and roseola infantum (Clemens, 1945) should be distinguishable. That of chickenpox and smallpox is clearly vesicular. Forchheimer (1898) described rose-red macules the size of a pinhead on the soft palate in rubella; a petechial eruption was seen in three of our cases in which the diagnosis was undoubtedly rubella. Glanzmann (1930) discussed the difficulties in distinguishing rubella and glandular fever. Petechiae may precede or accompany the vesicular lesions of herpangina (Huebner *et al.*, 1951; Kravis *et al.*, 1953) on the anterior tonsillar pillars and soft palate, as noted in our suggestive case.

Palatal lesions are not mentioned in clinical descriptions of a wide variety of illnesses which glandular fever may simulate: streptococcal and non-streptococcal tonsillitis, acute undifferentiated respiratory disease (Commission on Acute Respiratory Diseases, 1944, 1947), influenza (Horsfall, 1952), the typhoid group (Banks, 1949), brucellosis (Spink, 1956), infective hepatitis (Hoagland and Shank, 1946), lymphocytic choriomeningitis (Adair *et al.*, 1953), or any of the recently described benign meningitic or meningoencephalitic illnesses of viral origin (Acheson, 1954; Tyrrell and Snell, 1956; Lyle, 1956; Karzon *et al.*, 1965; Garnett *et al.*, 1957; Rotem, 1957).

More studies are needed to determine the frequency of the enanthem of glandular fever. Some find it in 5% of cases or less (Milne, 1945; Read and Helwig, 1945; Wechsler *et al.*, 1946; Hoagland, 1952), some in 25% (Stevenson and Brown, 1943; Berberich and Thomas, 1949), and Shiver *et al.* (1956) in 50% of sporadic cases. All our 28 patients with proved glandular fever had some palatal petechiae; 14 had more than five. In the same period the use of the screening procedure for heterophil antibodies, as described by Butt and Foord (1935), in at least 100 more of our patients revealed no other case in which subsequent investigation showed a diagnostic Paul–Bunnell reaction. The frequency of the enanthem in any given epidemic may well be misleading, as different epidemics are known to show different clinical (Tidy, 1934) and laboratory features (Shubert *et al.*, 1954).

The other lesions described occur occasionally in glandular fever but also in other diseases, although Leibowitz's white macules may be specific. The occurrence of petechiae with red or linear macules is, however, significant.

In conclusion, there is little doubt that the finding of multiple pin-point palatal petechiae in the absence of petechiae elsewhere or other palatal lesions is strong clinical evidence of glandular fever if rubella can be excluded. This should be of value in the diagnosis of cases of sore throat, adenopathy, skin rash, jaundice, lymphocytic meningitis, and polyneuritis.

Summary

The characteristic enanthem of glandular fever is an eruption on the palate consisting of multiple pin-point petechiae. If petechiae are few the sign is suggestive only.

The petechiae may occur from the 2nd to as late as the 26th day of the illness. Their duration is related to the duration of fever.

Other similar palatal lesions are discussed.

Our thanks are due to numerous colleagues for their help, in particular to Captains J. H. Adams, A. Addison, H. Baron, and O. W. Samuels, R.A.M.C., and to Miss Carla Tophoff for assistance in translation.

ADDENDUM.—Kendall *et al.* (*Brit. med. J.*, 1957, **2**, 131) describe petechiae on the soft palate and scanty atypical monocytes in pharyngo-conjunctival fever. It is possible that some of our cases with "no evidence of glandular fever" or "possible glandular fever" had this condition, though none had conjunctivitis.

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At a recent joint meeting of the British Tuberculosis Association with the Society of Medical Officers of Health, Dr. H. D. CHALKE, president of the Society, spoke of the changed role of the M.O.H. in tuberculosis, and emphasized the educative role of health visitors. He himself preferred the general purposes health visitor, although he agreed that a few specialized tuberculosis health visitors were very valuable as a nucleus based on chest clinics. He also commented on the hazards of allowing uncontrolled immigration and vagrancy, especially since for the first time within statistical record more people were coming into Britain than were leaving it. Dr. K. NEVILLE IRVINE discussed the value of B.C.G. vaccination and the useful ages at which this could be given. Although ideally the newborn child should be vaccinated, Dr. Irvine felt this was not practical and agreed with the present principle of vaccination before leaving school. He looked forward to the wider use of freeze-dried vaccine.

SERUM PROTEIN CHANGES FOLLOWING B.C.G. VACCINATION

BY

I. C. GILLILAND, M.D., F.R.C.P.Ed., M.R.C.P.
Lecturer in Medicine, Postgraduate Medical School; Physician, Prince of Wales's and St. Ann's Hospitals

PETER STRADLING, M.D., M.R.C.P.
Lecturer in Tuberculosis, Postgraduate Medical School; Physician, Hammersmith Chest Clinic

AND

E. M. ABDEL-WAHAB, M.D., Ph.D.
Research Assistant

From the Departments of Medicine and Chemical Pathology, Postgraduate Medical School, Hammersmith, London

A previous communication (Gilliland *et al.*, 1956) presented the results obtained by studying the serum protein of patients with pulmonary tuberculosis by the method of electrophoresis on paper. This study showed that the degree of change in the serum proteins was a measure of the severity of the systemic illness, and that the changes reverted to normal with recovery from the disease. This has since been confirmed by Leggat (1957).

Because of the difficulty in establishing the time of onset of tuberculous infections it was found possible to classify as "recent" only those in whom the infection was thought to be of less than six months' duration. The infections were usually severe enough to cause the patients to seek medical advice, so that minor degrees were seen infrequently.

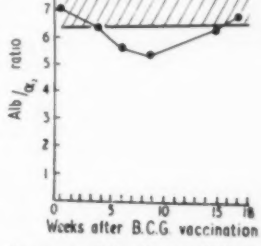
B.C.G. vaccination, however, provides both a known time of onset of the infection and a course which is considerably less virulent than clinical tuberculosis. It was therefore thought to be of interest to investigate serially the serum protein in a group of nurses receiving B.C.G. vaccination.

Method and Results

A total of 17 student nurses whose tuberculin tests were negative by the Heaf multiple puncture method volunteered to act as subjects for this investigation. Samples of blood were obtained before B.C.G. vaccination and at three-weekly intervals thereafter to 18 weeks. The site of vaccination was inspected on each occasion and a note made of any constitutional disturbance or intercurrent illness. The biochemical methods used were those detailed in the previous communication (Gilliland *et al.*, 1956).

All vaccinations took a normal course and the girls remained fit throughout.

The results are shown in the Table (overleaf), including the mean albumin/α_2 ratios and the standard errors of these means. The albumin/α_2 ratios are plotted in the Chart, and it will be seen that there is a decrease during the first eight to nine weeks followed by an increase back into the normal range. These changes are significant, being several times the standard error of the mean. Although the changes are not of great magnitude, they consistently affect



Serum protein changes following B.C.G. vaccination. Shaded area shows normal values.

the albumin and α_2 globulin levels and are therefore reflected to the maximum by taking the ratio between these two proteins.

Mean Values of Serum Proteins

	Before	Weeks after Vaccination				
		3	6	9	15	18
Albumin	4·20	4·28	3·91	3·83	3·83	4·11
α_1	0·36	0·37	0·35	0·37	0·41	0·35
α_2	0·63	0·68	0·70	0·73	0·64	0·64
β	0·90	0·73	0·64	0·73	0·84	0·86
γ	1·28	1·23	1·19	1·24	1·36	1·29
Albumin/α_2 ratio	6·84	6·31	5·63	5·37	6·04	6·45
Standard error of mean	±0·29	±0·17	±0·14	±0·15	±0·19	±0·20

Conclusion

One of the problems apparent from our previous investigation was the lack of a strict measure of the sensitivity of our test. The clinical assessment of the patients must of necessity be a rough yardstick, depending more on subjective human observations than the albumin/α_2-globulin ratio obtained from serum electrophoresis. The date of infection was also impossible to determine in most cases.

Hudgins *et al.* (1956) showed that B.C.G. inoculation produced changes in serum protein in rabbits and guinea-pigs at an interval of four weeks. B.C.G. vaccination of healthy adults produces a short-lived mild tuberculous infection which has nevertheless yielded definite and consistent serum protein changes. It is concluded that not only can the albumin/α_2-globulin ratio mirror accurately small changes occurring in mild infections but that these changes appear early in such infections.

We would like to express our thanks to the nurses who volunteered to take part in this study, and to Miss Godden, the matron of Hammersmith Hospital, for her co-operation.

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Medical Memorandum

Ruptured Dissecting Aneurysm of Abdominal Aorta Simulating Obstruction of Large Bowel

Dissecting aneurysm of the abdominal aorta is a protean disease. Its symptoms vary according to the site and direction of the dissection and the branches involved. As a rule the electrocardiograph shows signs of previous involvement of the heart and coronary vessels, and arterial hypertension is common.

Sudden epigastric pain, collapse, and shock, combined with haematemesis or melaena (due to involvement of the gastric or mesenteric arteries) or with haematuria (renal arteries) progressing to uraemia and anuria (Jellinek, 1956), are signs of dissecting aneurysm. Evidence of progressive internal haemorrhage and the detection of an abdominal mass, which may pulsate or even increase in size during observation, should lead to a suspicion of ruptured aortic aneurysm. Abdominal ecchymoses are a late sign, which should clinch the diagnosis. A plain radiograph of the abdomen is often of some help. There may be signs of paralytic ileus due to involvement of the mesenteric vessels and retroperitoneal dissection, but cases presenting as an obstructive lesion of the colon are sufficiently rare (Cuny, 1937; Mayo, 1951) to warrant the report of the following case.

CASE REPORT

A somewhat demented lady of 83 was admitted to Frederiksberg Hospital on February 5, 1953, in a state of shock. In 1941 she had had a small cerebral haemorrhage resulting in a left-sided facial paralysis. Practically no sequelae had followed, but there had been some mental deterioration during the last six months.

Two days after admission, and after resuscitation with dextran and blood transfusions, she complained of abdominal pain, and a surgeon was called. On examination the abdomen was distended and tympanitic, with "metallic" borborygmi on the left side and tenderness on the right side. There was arterial hypertension, and an electrocardiogram showed left axis deviation and signs of myocardial degeneration. A pelvic examination revealed a hard rounded tumour in the midline, the size of a grape-fruit. She was transferred to Surgical Department A for further observation, and *x*-ray studies were carried out. A plain *x*-ray picture showed a dilated air-filled colon. The next morning radiographs showed dilated coils of bowel in the lower right quadrant, with fluid levels visible in the radiographs taken with the patient erect. A partially calcified rounded shadow was seen in front of the lower three lumbar vertebrae. As bowel action had stopped and radiological signs of colonic obstruction had developed, an exploratory laparotomy was contemplated. However, a rapid deterioration of her condition set in, and she died on February 8.

At necropsy the principal findings were: severe atherosclerosis of the aorta (a coincident syphilitic aortitis could not be excluded) and coronary arteries, a large aneurysm of the abdominal aorta with a secondary dissecting aneurysm which had ruptured, a large collection of blood under the diaphragm, and a fibromyoma of the uterus. The Wassermann reaction was positive, but this information became available only after death.

COMMENT

Osler (1905) reported that aneurysms of the abdominal aorta accounted for about 1 in 1,000 admissions to Johns Hopkins Hospital. Since then the number of syphilitic aneurysms (most frequent in the younger patients) has decreased, while the incidence of arteriosclerotic aneurysms has increased. The prognosis has been determined by Estes (1950): in his series, comprising all cases of abdominal aortic aneurysm seen at the Mayo Clinic, 67% survived for more than a year and 49% for more than three years. Once symptoms appear—they probably indicate the start of a leak—most patients survive for less than a year. This is borne out by the fate of the three other patients with aneurysms of the abdominal aorta admitted to Surgical Department A during the last six years: (1) A man of 72 died 24 hours after admission owing to rupture and the formation of an extensive retroperitoneal haematoma. (2) A man of 66 with a dissecting ruptured aneurysm had an emergency exploratory laparotomy because an internal strangulated hernia was suspected; he died four days later. (3) A man of 54 had an exploratory laparotomy because of a cystic abdominal tumour, the tentative pre-operative diagnosis being a pancreatic or mesenteric cyst. At operation the correct diagnosis became evident, but he died suddenly six months later.

The present treatment of choice of aortic aneurysm is excision and the insertion of an aortic homograft or an "ivalon" prosthesis (De Bakey and Cooley, 1953; Kirklin *et al.*, 1953; Kinmonth *et al.*, 1955). Ruptured aneurysms have also been successfully excised. In the case described above such an operation would not have been warranted even if facilities for its performance had existed.

ERIK CHRISTENSEN, M.B., B.S.,
Surgical Department A, Frederiksberg Hospital, Copenhagen.

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Reviews

TREATMENT OF BURNS

The Treatment of Burns. By Curtis P. Artz, M.D., F.A.C.S., Lieut.-Col., M.C., U.S.A. (Ret.), and Eric Reiss, M.D. Illustrations by Burr Bush. (Pp. 250+xii; illustrated. 52s. 6d.) Philadelphia and London: W. B. Saunders Company. 1957.

This book is the first full-scale general account of the treatment of burns to appear in English for several years. It is largely based on the intensive experience of these injuries at the U.S. Army Surgical Research Unit, Brooke Hospital, San Antonio, Texas. Many of the patients there are previously healthy young men burned in Service conditions, often in aircraft or transport accidents. In contrast, severe burns in British civilian practice are usually of children and elderly ladies and result from clothes catching fire in the home. In spite of these differences it is striking how similar to opinion here is the appraisal by the authors of current problems of burns therapy. Throughout the book an admirably critical approach to the various claims and counter-claims of opposing opinion is maintained. For instance, the respective merits of both exposure and closed treatment are considered. In this context it should perhaps be remembered that San Antonio is in a more southerly latitude than any part of Europe and has a climate particularly suited to drying and comfort of exposed areas. An unusual feature of the treatment described is that the formula for fluid replacement provides three times as much saline as colloid. It is not easy to see the rationale for this, since, as stated on page 31, burn exudate contains about 4% plasma protein with normal electrolyte complement. The effective concentration of the recommended replacement fluid is about 2% protein. Since renal sodium retention is so marked in burned patients, there would seem some hazard in giving such large quantities of saline. It will be interesting to see later reports of results with the Brooke regimen. The authors emphasize the predominant importance of infection as a cause of death, and they report a high proportion of septicaemia, chiefly due to *Staphylococcus aureus* or *Pseudomonas pyocyanea*, among fatal cases. Nutrition, the other great problem of the later care of extensively burned patients, is also very adequately considered. The advice given throughout this book is practical and based on careful appraisal of evidence with a welcome freedom from dogmatism and exaggerated claims. It can be recommended to all concerned with learning about or treating burns.

J. P. BULL.

MICROSCOPICAL EXAMINATION OF TISSUES

Histological Technique for Normal and Pathological Tissues and the Identification of Parasites. By H. M. Carleton, with the collaboration of R. A. B. Drury. Third edition. (Pp. 343+xvi. 30s.) London, New York, Toronto: Oxford University Press. 1957.

Biology Staining Schedules for First Year Students. By R. R. Fowell, M.Sc. Fifth edition. (Pp. 27. 2s. 6d.) London: H. K. Lewis and Co. Ltd. 1957.

A third edition of *Histological Technique*, written by the late H. M. Carleton with the collaboration of R. A. B. Drury, has just been published. This book, the first edition of which appeared in 1926, is now well established; it can be found in most laboratories concerned with the histological examination of tissues, and is regarded as a necessary and reliable guide in work of this kind. With little increase in size many changes have been made in order to bring the new edition up to date. Some sections have been omitted; a certain amount of rearrangement has been made; and in many parts the text has been rewritten. In the chapters on methods of histological examination a more detailed account is given of the polariscope and its uses. There is a short note on phase-contrast microscopy, but a fuller account of the fluorescent technique. There is also a description of the electron microscope and its advantages and disadvantages. Dr. Drury has contributed new chapters on methods of histopathological processes, bacteriological methods, and methods for spirochaetes. Some of the recent staining techniques have been introduced, such as the periodic-acid–Schiff test for carbohydrates—now being used on an increasing scale. No mention is made, however, of the methods for demonstrating acid and alkaline phosphatase, and one or two illustrations in colour might have been included with advantage. The book still retains certain qualities which maintain its value. It is written in a clear and concise manner. In many instances the relative merits of different techniques are noted by the authors or some other competent authority, and practical hints are given on many details so that the best results may be obtained. For these reasons this edition should be well received by laboratory workers.

The small manual entitled *Biology Staining Schedules for First Year Students*, by R. R. Fowell, has just appeared in its fifth edition. This is intended for students in first-year science courses and explains in simple language the nature of the processes used in the preparation of stained specimens for microscopical examination. In this edition the symbols, chiefly those for weights and measures, have been revised in accordance with modern practice. It is an easy book to read and understand and well suited for the purpose for which it was written.

J. BAMFORTH.

TECHNIQUES OF PSYCHOTHERAPY

A Short History of Psychotherapy in Theory and Practice. By Nigel Walker, Ph.D. (Pp. 185+xii; illustrated. 25s.) London: Routledge and Kegan Paul. 1957.

What does the psychotherapist—Freudian, Jungian, Adlerian, or hypnotist—really do with his patients? The author sets out to answer this problem. He assumes that psychotherapy is neither an art nor a science, but a technique; that is, a collection of rules for achieving a certain objective—here the treatment of psychogenic disorders. Consequently he traces the development of the different techniques. With the exception of the suggestionists and those who accept Pavlov's doctrines, the technique of Freud is regarded as the source of all techniques in the schools of psychotherapy which succeeded him. Yet the author makes the odd claim that, in technique, the modern schools of psychotherapy, including the Freudian, are descended from the curative technique of Mesmer. The technique of, say, the Adlerians, despite its distinctiveness, should be thought of as an intermediate or perhaps a sub-technique of the Freudian. New techniques and innovations in psychotherapy are few, according to the standards set by the author, and many well-known names—for instance, Finesinger's—are omitted. There is a clever epitome of orthodox psycho-analysis and post-Freudian psycho-analysis, particularly the teaching of Mrs. Klein. Adler's Individual Psychology and Jung's Analytical Psychology are also surveyed, but rather cursorily. Several inaccuracies have crept in. The grounds for Jung's divergence from Freud are well known, and so it is disappointing to find here the oft-repeated, but erroneous, notion that Jung broke with Freud as an escape from Freud's emphasis on sexuality. Again, free-association, we are told, is rarely used by Jung except to supplement picture painting. Jung never uses free-association. The author has confused Jung's method of association (amplification) and Freud's free-association. The emphasis throughout is upon the importance of techniques, and little attention is paid to differences in theory of those using the techniques. Nevertheless, Dr. Walker agrees that the personal traits of a psychotherapist are of most importance in effecting the success of treatment. He anticipates that the incommunicable element in treatment will become a technique. Few practising psychotherapists will share this expectation.

E. A. BENNET.

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PRIMARY DRUG RESISTANCE IN TUBERCLE BACILLI

Patients who excrete drug-resistant tubercle bacilli in their sputum may have acquired them in one of two ways: they may have been originally infected with drug-sensitive organisms which, having been successfully eliminated by chemotherapy, have been replaced by drug-resistant mutants, or they may have been infected from the start with drug-resistant organisms. How common are such infections? Do they occur "naturally" in the absence of contact with previously treated patients, or do they arise only when there has been contact of this kind? What is the importance of infection with drug-resistant tubercle bacilli, both epidemiologically and in its effect on the clinical progress of individual patients? Some of these questions are answered in a recent survey[1 2] of the incidence of drug-resistant tubercle bacilli in untreated patients carried out by a group of Medical Research Council workers. The first of these reports records the prevalence of primary drug resistance in newly diagnosed patients with pulmonary tuberculosis. A randomly selected sample of chest clinics in Great Britain provided the patients for this survey, which took place between June 15, 1955, and March 8, 1956. The specimens of sputum were sent by post to a central laboratory: it was hoped that this would ensure uniformity in the techniques used and in the interpretation of results. The positive cultures numbered 974, and 50 of these (5.1% of the total) were resistant to one or more of the three commonly used drugs—*para*-aminosalicylic acid (P.A.S.), streptomycin, and isoniazid. Six of the resistant cultures were atypical mycobacteria, and 44 (4.5%) were typical drug-resistant tubercle bacilli. The results showed that during the period of the survey "2.3% of newly diagnosed and previously untreated patients with pulmonary tuberculosis were infected with streptomycin-resistant tubercle bacilli and 2.2% with P.A.S.-resistant organisms. . . . Only 0.7% of the patients, however, were found to yield isoniazid-resistant organisms." Analysis of age and sex differences showed that, whereas the overall incidence of drug resistance was 5.1%, in women under 35 it was 9.3% and in older women 4.9%; while in men under 35 it was 3.0% and in older men 4.1%. Contact histories were studied in the 44 patients infected with drug-resistant tubercle bacilli and in a similar group of 44 patients infected with sensitive tubercle bacilli. Definite evidence of contact with organisms resistant to the relevant drug was found with streptomycin in 3 out of 22 patients, with P.A.S. in 5 out of 21 patients, and with isoniazid in 2 out of 7 patients. In the corresponding group of "drug-sensitive" infections no evidence of contact with resistant organisms was found.

In the second report of this survey D. A. Mitchison and J. B. Selkon report on its bacteriological aspects. When tubercle bacilli of rather low degrees of drug resistance are being investigated it is often impossible with any single test to say whether the result indicates a true resistance or is within the limits of experimental variation of the methods used. From the data obtained from a large number of sensitive cultures Mitchison and Selkon were able to define resistance ratios, and to calculate the probability that a sample could have been drawn from the fitted normal distribution of results on sensitive strains. A probability of 2 in 10,000 or less was arbitrarily taken as resistant, and a probability of 3 in 1,000 or more as sensitive. Thus the definitions of drug sensitivity and resistance used in the survey are purely statistical. Some of the difficulties inherent in this method of judging the resistance of cultures are fully discussed by the authors.

The survey then answers some questions but raises others. It suggests that about 1 in every 20 cases of previously untreated pulmonary tuberculosis is infected with "drug-resistant" organisms, or at least with organisms which depart significantly from the average range of drug sensitivity which can be accepted as normal. But whether these levels of resistance are significant clinically and epidemiologically is not known at this stage. Some of the evidence on this point has been reviewed by Mitchison,[3] but more information is needed on the subsequent progress of patients with low degrees of drug resistance when treated with the relevant drug. It is certainly true that the development of obvious drug resistance during treatment is associated with clinical deterioration, and that patients who excrete highly resistant organisms no longer respond to continued treatment with the drug.[4] But the position is not so clear with organisms of low resistance, and it is important to

[1] Fox, W., Wiener, A., Mitchison, D. A., Selkon, J. B., and Sutherland, I., *Tubercle*, 1957, **38**, 71.
[2] Mitchison, D. A., and Selkon, J. B., ibid., 1957, **38**, 85.
[3] —— *Brit. med. Bull.*, 1954, **10**, 115.
[4] Wormsam, A. R. H., Collard, P., Carroll, J. D., and Knox, R., *Tubercle*, 1956 **37**, 73.

know at what level of resistance it is reasonable to assume that further treatment with a drug will be useless.

The comparatively low incidence of resistance to isoniazid revealed by the survey is interesting, but its real meaning is very doubtful. The authors suggest several possible explanations, but none of them is very convincing. At the time of the survey isoniazid had been in use for four fewer years than the otner two drugs. But other factors must be considered, such as relative avirulence of some isoniazid-resistant strains and changes in the frequency and duration of combined chemotherapy. It will be interesting to see in the course of the next few years whether the incidence of isoniazid resistance increases cumulatively or whether as a result of rational combined chemotherapy the incidence of resistance to all three drugs declines. Since the frequency with which resistance develops to one drug is very largely dependent on the extent to which it has been used in combination with other drugs, the whole situation may be profoundly altered by the discovery of new antituberculous drugs: the result might be a very rapid decrease in the frequency of drug resistance developing during treatment, and, as a result, a still further reduction in the frequency of drug resistance in untreated contact cases.

The whole picture of tuberculosis in Britain is changing quickly from year to year. Deaths have fallen from 23,551 in 1947 to 5,573 in 1956, and notifications, which started to fall much later, are now also steadily decreasing. The problem of drug resistance in tuberculosis is by no means solved, but it looks as though it is not going to prove so serious a menace as was feared, and that it is not even now exerting any serious delaying effect on the eradication of the infection.

ATRIAL SEPTAL DEFECT

The prospect of definitive surgical treatment has encouraged closer study and increased understanding of defects of the atrial septum. A defect of this type was found in 18% of P. Wood's[1] 900 cases of congenital heart disease; it is the commonest single congenital cardiac malformation met in clinical practice. D. E. Bedford and his colleagues[2] at the Middlesex Hospital have described the three main types of defect. The persistent ostium primum defect overlies the orifice of the tricuspid valve, the lower margin being formed by the ventricular septum and by the mitral and tricuspid valves, which are often malformed. An associated ventricular septal defect may be present, or there may be a common atrioventricular canal. The persistent ostium secundum or fossa-ovalis defect lies higher than the ostium primum and does not involve the atrioventricular valves. Defects may be small or large, single or multiple, or fenestrated. The larger defects may extend to the orifice of the inferior vena cava and lie astride the caval orifice, which may empty partly into the left atrium if there is a large Eustachian valve. The third type of defect is above the fossa ovalis and immediately below the superior vena cava. More than one type of defect may coexist, and one or more anomalous pulmonary veins may drain into the right atrium or venae cavae, as in 10% of the Middlesex Hospital cases.

The septal defect results in the passage of blood from the left to the right atrium (left-to-right shunt), and the size of this shunt is proportional to the size of the defect. The pressure is greater in the left than in the right atrium when the shunt is small, but equal when the shunt is large, when blood streams from left to right atrium because of the greater distensibility of the right than of the left ventricle in the face of equal filling pressures.[3] The addition of the left-to-right shunt to the normal output of the right ventricle increases the stroke volume and leads to dilatation and hypertrophy. Pulmonary plethora results from the increased pulmonary blood flow. Enlargement of the right atrium and pulmonary artery follow, and sometimes the pulmonary valve becomes incompetent. Since the right atrium "steals" part of the left atrial inflow, the output of the left ventricle is diminished. The pulmonary vascular bed has normally a low resistance, so that an increased pulmonary blood flow can exist with little rise in pulmonary arterial pressure in the uncomplicated case. If pulmonary stenosis is present as an additional anomaly, it may be severe and cause reversal of the left-to-right shunt and thus dominate the clinical picture. If mild, the diagnosis of pulmonary stenosis is difficult.[4] Significant mitral stenosis is much less common than originally thought,[5-7] but mitral incompetence may occur with septum primum defects. Additional anomalies may be present, such as drainage of one or more pulmonary veins into the right atrium.

[1] Wood, P., *Diseases of the Heart and Circulation*, 2nd ed., 1956. London.
[2] Bedford, D. E., *et al.*, *Lancet*, 1957, **1**, 1255.
[3] Dexter, L., *Brit. Heart J.*, 1956, **18**, 209.
[4] Rudolph, A. M., Nadas, A. S., and Goodale, W. T., *Amer. Heart J.*, 1954, **48**, 808.
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[10] Walker, W. J., *et al.*, *Amer. Heart J.*, 1956, **52**, 547.
[11] Rossall, R. E., and Gunning, A. J., *Lancet*, 1956, **1**, 604.
[12] Canada, W. J., Goodale, F., Jr., and Currens, J. H., *New Engl. J. Med.*, 1953, **248**, 309.
[13] Swan, H. J. C., Burchell, H. B., and Wood, E. H., *Circulation*, 1954, **10**, 705.
[14] —— *et al.*, ibid., 1957, **16**, 54.
[15] Doyle, A. E., *et al.*, *Brit. Heart J.*, 1957, **19**, 353.
[16] Campbell, M., Neill, C., and Suzman, S., *Brit. med. J.*, 1957, **1**, 1375.
[17] Burrett, J. B., and White, P. D., *Amer. J. med. Sci.*, 1945, **209**, 355.

Patients with small defects, and many with larger uncomplicated ones,[2] are symptomless for many years, although the latter may develop symptoms in the third decade. Intolerance of effort is the cardinal symptom and may be due more to tiredness than to dyspnoea. Palpitations (due to supraventricular arrhythmias) are common. Recurrent respiratory infections, haemoptysis, and precordial pain may also occur. The arterial pulse is small, and the diffuse, heaving cardiac impulse which lifts the sternum indicates a hyperdynamic right ventricle. The second heart sound is widely split owing to delay in closure of the pulmonary valve, and the split fails to widen on inspiration.[5 8] A pulmonary ejection systolic murmur and click are common, and a high-pitched early diastolic murmur due to pulmonary incompetence may occur. Increased flow through the tricuspid valve causes a loud first sound, a mid-diastolic murmur heard on inspiration in the tricuspid area, and a right atrial systolic murmur.[3] This mid-diastolic tricuspid murmur has in the past been erroneously ascribed to additional mitral stenosis. The jugular venous pressure may be normal, but is often slightly raised, and the pulse form shows equal "a" and "v" waves. In children, the "v" wave is prominent and is preceded by an exaggerated "x" descent.[9] Many patients are slender in build, with a high arched palate and arachnodactyly. Kyphoscoliosis and bulging of the sternum are also often seen.

The cardiogram shows some form of right bundle branch block in most cases, the incidence varying from 95%[8] to 66%.[10] Radiologically there is enlargement of the right atrium, right ventricle, and pulmonary artery, the last often being very distended, or even aneurysmal, and is in striking contrast to the small aortic shadow. There is obvious pulmonary plethora. Horizontal costophrenic lines are rare,[11] since the left atrial pressure is not usually appreciably raised.

The complications of atrial septal defect are failure of the right ventricular myocardium as a result of chronic overloading, leading to progressive cardiac enlargement and tricuspid incompetence; atrial fibrillation (10%)[2]; and progressive reductions in the pulmonary vascular bed causing an increase in resistance (which has been termed obstructive pulmonary hypertension) and reversal of the left-to-right shunt. Thrombosis of the major pulmonary arteries may also occur.[2 12] Central cyanosis and clubbing of the fingers are due to the development of a right-to-left shunt as a result of a greatly increased pulmonary vascular resistance or of severe pulmonary stenosis, but slight degrees of arterial desaturation may be due to streaming effects from caval veins to left atrium[13 14] in the absence of either of these complications. Obstructive pulmonary hypertension occurred in 15% of the Middlesex and in 20% of Wood's cases. The cause of the obstructive changes in the small pulmonary blood vessels is unknown. Severe obstructive pulmonary hypertension modifies the clinical picture. Central cyanosis and clubbing occur, the "a" wave of the jugular venous pulse increases in size, the second heart sound becomes less widely split and the pulmonary component accentuated. The pattern of right bundle branch block is replaced by one of severe right ventricular hypertrophy. Radiologically, the peripheral lung fields often become clearer, although this sign may be misleading.[15] A similar picture occurs with severe pulmonary stenosis, with the difference that the pulmonary component of the second heart sound is soft and late, and a loud ejection murmur is heard over the pulmonary artery. Lesser degrees of pulmonary hypertension occur as a result of a very large pulmonary blood flow, the pulmonary vascular resistance being normal. This has been termed hyperkinetic pulmonary hypertension.[1]

The diagnosis of atrial septal defect can normally be made clinically, but cardiac catheterization is required to decide the size and site of the defect, the magnitude of the shunts, and the level of pulmonary vascular resistance. In uncomplicated cases the blood from the right atrium has a greater oxygen saturation than that of the caval veins, the pulmonary blood flow is greatly increased, and the pulmonary artery pressure is normal or only slightly raised. If there is obstructive pulmonary hypertension, the left-to-right shunt is smaller, and a right-to-left shunt may be present. Anomalous pulmonary venous drainage may be detected by passage of the catheter from the right atrium into a pulmonary vein. Tests with dyes have been used to confirm the left-to-right shunt and to locate the site of the defect.[14]

In a recent article in this *Journal* M. Campbell, C. Neill, and S. Suzman[16] attempted to assess the course and prognosis of atrial septal defect from a study of 100 cases. After infancy had been passed most of their patients could lead nearly normal lives for the next two decades, and 85% of them were still doing well at 30 years of age. But the prognosis became much worse in the fourth and fifth decade of life. However, though many patients remain symptomless for years, others develop symptoms in early life.[7] The average age of death is 37 years.[17] Serious cardiovascular changes are apt to occur after the age of 20 years, and great cardiac enlargement is present in more than 50% of patients after the age of 40.[2] The occasional finding of patients in the sixth and seventh decades with atrial septal defect in no way

invalidates the serious nature of the lesion in the majority. Effective surgical repair in early life before important changes in myocardium or lungs have occurred is therefore greatly to be desired. The era of safe and effective surgery for atrioseptal defect is very near, and in the next few years closure of uncomplicated defects is likely to become the routine procedure that ligation of patent ductus arteriosus has become and resection of coarctation is quickly becoming.

DETERMINING SEX

During 1932–49 V. N. Shreder (sometimes spelled "Schröder") recorded in a remarkable series of papers[1–11] how, by means of electrophoresis, she separated rabbit spermatozoa which migrated towards the anode from those which migrated towards the cathode. When she inseminated female rabbits with anode-migrating spermatozoa the offspring were mostly female, while the cathode-migrating spermatozoa produced mostly males. Her results showed a successful prediction of sex in 80% of the cases. Another Russian worker, A. A. Siljander,[12] repeated Shreder's work and also found that the cathode-migrating spermatozoa gave a preponderance of males, but anode-migrating spermatozoa produced a sex ratio not significantly different from that of controls. Two other workers also attempted to reproduce Shreder's results. A. Pilz[13] was unable to obtain any electrophoretic separation of sperm and therefore did not proceed further. E. Kordts[14] did obtain separation, but he did not notice any significant difference in the sex ratio by insemination of the two separated fractions.

A paper giving references to this earlier work and reporting a new investigation has now appeared from the Department of Zoology of the University of California, Berkeley; it is sponsored by the eminent geneticist Professor Curt Stern. In it M. J. Gordon[15] reports that he separated rabbit spermatozoa into cathode- and anode-migrating fractions. He inseminated female rabbits after producing ovulation by means of mechanical stimulation, hormonal injection, or by mating the doe to a vasectomized buck just before insemination. From 201 inseminations 31 litters were obtained. Because of the risk of cannibalism by the female parent, the newborn offspring were removed as soon as possible and killed during the first or second day after birth. The gonads were dissected out and the sex determined histologically. Elaborate "blind" tests were performed to ensure that the histological diagnosis was made without bias. The result was that the anode sperm produced 62 females and 25 males and the cathode sperm produced 29 females and 51 males. This difference is highly significant (χ^2 20.62, with $P<0.001$). It was also noteworthy that, with the exception of one litter consisting of only one offspring, all the unisexual litters were of the same sex as predicted. From insemination with cathode sperm 4 out of 14 litters were all male, while from insemination with anode sperm 3 out of 17 were all female.

The author discusses at some length possible explanations of why a sperm carrying an X chromosome should have a different isoelectric point from one bearing a Y chromosome. V. M. Ingram's[16] work on the differences between sickle-cell and normal haemoglobin throws light on this. Here the differences in a single amino-acid of one of the two protein chains forming the globin part of haemoglobin causes notable changes in electrophoretic mobility. The surface charge of spermatozoa may be influenced by the composition of the interior nucleo-proteins. It is even possible that the separation of the spermatozoa by electrophoresis is not based on differences in surface charges. Shreder[9] noted a temperature effect on the direction of migration. At higher temperatures the direction of migration is reversed. Gordon thinks that this may be an indication that the electric charges are on materials other than surface proteins. At certain temperatures the surface membranes, which are normally acting as electrical insulators, may lose this property and then act as conductors, so that internal particles having charges may be responsible for the migration. The spermatozoa move on electrophoresis with their tails in front, and the electron microscope studies of J. Schultz-Larsen and R. Hammen[17] have indicated that head and tail should be regarded as a single unit. With admirable caution Gordon concludes his article by stating that "a final establishment of this work depends, of course, on continued investigations."

One cannot but speculate on what consequences such work, if successfully developed, would have in both animal breeding and the planning of human families. If human parents become able to determine the sex of their children, would the size and sex ratio of human populations change? Parental preferences for boys and girls may be fairly evenly divided, at least in contemporary Great Britain, since M. H. Thomas[18] has shown that parents who have had two children of the same sex are more likely to have a third than are parents who have had two of opposite sex. In contrast, a bellicose society might deliberately encourage the breeding of potential soldiers, or a luxurious society the breeding of potential domestic servants. On the whole, this looks like being one of those decisions better left to nature, but unlikely to be.

SYRINGE SERVICES

It is an unfortunate fact that some of the implements most widely used in medicine are among those most difficult to sterilize. Syringes are an example of this. They cannot be adequately and conveniently sterilized by the user, since neither boiling nor any feasible

[1] Shreder, V. N., *Biol. Z.*, 1932, **1**, 24.
[2] —— ibid., 1934, **3**, 465.
[3] —— ibid., 1936, **5**, 657, 690.
[4] —— ibid., 1937, **6**, 1235.
[5] —— *Chem. Zbl.*, 1937, **2**, 3180.
[6] —— ibid., 1939, **2**, 1293.
[7] —— *Bull. Acad. Sci. U.R.S.S. Ser. biol.*, 1940, 426.
[8] —— *C. R. Acad. Sci. U.R.S.S.*, 1940, **26**, 692.
[9] *Z. Tierz. Zücht.-Biol.*, 1941, **50**, 1, 16.
[10] *Chem. Zbl.*, 1943, **2**, 430.
[11] *Usp. sovre. Biol.* (*Moscow*), 1949, **28**, 211.
[12] Siljander, A. A., *Sborn. Trud. Zootek. Kaf. s.h. Skot. Kirov.*, 1936, 148.
[13] Pilz, A., *Z. Tierz. Zücht.-Biol.*, 1952, **60**, 315.
[14] Kordts, E., ibid., 1952, **60**, 221.
[15] Gordon, M. J., *Genetics*, 1957, **43**, 913.
[16] Ingram, V. M., *Nature*, 1956, **178**, 792.
[17] Schultz-Larsen, J., and Hammen, R., *Dan. med. Bull.*, 1956, **3**, 141.
[18] Thomas, M. H., *Brit. med. J.*, 1951, **1**, 733.

chemical treatment is fully effective. Moreover, a syringe, to be in perfect condition for use, should be dry and lubricated, and in a container protecting it from contamination; it should also have been chemically cleaned after previous use, and its needle should have been sharpened by an expert. These advantages can be secured only when the provision of syringes becomes a separate job. Recognizing this, some hospitals have established a syringe service, which may or may not be part of a department providing sterilized equipment of other kinds. When the duties of such a department are more extensive, it may be a regular part of a nurse's training to serve there, thus countering the objection that such centralization deprives her of necessary experience.

Any hospital or hospital group which is contemplating the establishment of a syringe service pure and simple will find all the necessary information and admirable advice in a booklet[1] recently published by the Nuffield Provincial Hospitals Trust. The Trust was invited by the Ministry of Health to conduct an inquiry into the organization of such a service, with particular reference to costs. It appointed an operational research unit under the direction of Brigadier J. D. Welch, which studied three existing syringe services of different sizes, one serving a single hospital, another three, and the third a large area. The report makes recommendations on accommodation and lay-out, staff, equipment, types of syringe, packing and sealing, procedures in washing, drying and assembly, storage and issue, and record-keeping. Three methods of sterilization are referred to. Autoclaving is not recommended, and the standard method is the hot-air oven fitted with a fan to circulate the air and thus ensure uniformity of temperature; this also requires the oven to be so loaded as to leave a space round each syringe. The third method is the radiant heat oven with infra-red elements through which syringes pass on a moving belt, thus attaining a higher temperature for a shorter time. This new type of sterilizer, which has recently been fully described by E. M. Darmady and colleagues,[2] has advantages for a unit with a large output.

A chapter is devoted to costs, which are analysed in some detail—both the initial outlay and the running costs. Though wages, which are exactly specified for each class of operative, are the largest item, syringe replacements account for 26–29% of the total. The annual cost of services providing 500 or 1,000 syringes a day is given as £3,725 and £6,800. It is interesting that very large services are not thought likely to be more economical, because transport over greater distances will diminish the rate of turnover. An appendix gives particulars of all items of equipment and the sources from which they can be obtained. This publication is thus a complete guide to the establishment and running of a syringe service, and will doubtless encourage their much wider development. Large hospitals may well consider whether this is as far as they need go, or whether the provision of syringes should be only one function of a central supply service for sterile equipment. Inefficiently sterilized syringes are not alone in having caused deplorable infective accidents: some of the worst of these have been due to unsterile apparatus used for lumbar puncture.

[1] *The Planning and Organization of Central Syringe Services*, 1957, The Nuffield Provincial Hospitals Trust, Nuffield Lodge, Regent's Park, London, N.W.1, price 2s. 6d.

[2] Darmady, E. M., Hughes, K. E. A., and Tuke, W., *J. clin. Path.*, 1957, **10**, 291.

INTERNATIONAL CLASSIFICATION OF DISEASES

In an attempt to ensure uniformity in the classification of disease an International List has long been used by epidemiologists and by public health and Government departments. Dr. William Farr, of the General Register Office, first urged the adoption of a uniform classification over a century ago,[1] and it was largely as a result of his work that the International Statistical Congress in 1855 adopted a list of 139 "rubrics" of causes of death which has survived to the present day as the basis of the International List. In 1899 the International Statistical Institute recommended the universal adoption of a revised classification in all statistical institutions, and recognized the necessity for decennial revision of the list in order to keep pace with the advances of medicine. Since that date there have been seven conferences for the revision of the International List, and the results of the deliberations of the latest have just been published.[2] The International List consists of 612 categories of diseases and morbid conditions, 153 categories for classification of the external cause of injury, and 189 categories for characterization of injuries according to the nature of the lesion: these categories are grouped into 109 summary groups which in turn are further grouped under 17 main headings—infective and parasitic disease, diseases of the respiratory system, etc. In addition there is a supplementary classification allotted to the recording of persons who, for example, are admitted to hospital but are not sick: this includes categories for causes of stillbirth which are not yet registered in England and Wales.

The sixth revision,[3] published in 1949, broke new ground, in that for the first time it made provision for the classification of both morbidity and mortality data. The sixth revision conference also approved the International Form of Medical Certificate of Cause of Death based on that used in England and Wales since 1928.

It has been decided that the seventh and subsequent revisions of the International List be published in time to be applied to mortality statistics at the beginning of years ending in "8," so that countries may obtain sufficient experience in its use before the next census. The sixth revision came into use in most countries in 1950, and because of the comparatively short period that has elapsed since its introduction, and also because of the radical changes made in it, the seventh revision conference decided to limit the current revision to essen-

[1] Registrar-General of England and Wales, *Sixteenth Annual Report, 1956*, Appendix pp. 75–76, H.M.S.O., London.

[2] *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* (Seventh Revision), 1957, W.H.O., Geneva.

[3] *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death* (Sixth Revision), 1948–9, W.H.O., Geneva.

tial changes and amendment of errors and inconsistencies. It is a tribute to the work of the previous conference that virtually no major changes were found to be necessary in the present revision. Nevertheless there have been a large number of minor changes, and regular users of the International Classification—medical officers of health, epidemiologists, medical records officers, and so on—will find it to their advantage to obtain the new manual rather than to try to make do for the next ten years with an amended copy of the old one. We understand that the General Register Office, in adopting the new revision from January 1, 1958, will follow their usual practice and measure the effect of the change by coding causes of death according to both the sixth and seventh revisions of the International Classification. As yet, only the first volume of the classification has been published. The second volume, which contains an index of terms with a reference to the place of each term in the classification, will be published shortly.

Many of the advances of medicine come from an examination of facts which have been collected and accurately classified. In the past the International List has been of great assistance in the classification of disease. The present revision will continue the tradition.

ALLERGY TO MILK

Enthusiasm is a great driving force, and allergy is one of the subjects which engenders enthusiasm among its devotees. As the allergic "diathesis" is largely inherited it is not surprising that overt manifestations of the condition appear mainly in infancy or early childhood. The youngest reported case is that of foetal hiccups.[1] The common toxic erythema seen in so many newborn infants is thought by some to be an allergic manifestation, but, if it is, it is very temporary and allergy must be very widespread. Colic is another frequently encountered disorder in infants; it is a great temptation to the allergist, though there are many other possible causes. In eczema the position is clear; it is indeed an allergic condition, and confirmation comes from the subsequent history. Infantile eczema is rarely seen before the age of 2 months, but at this age a food allergen is a reasonable hypothesis, and, if weaning has not been started, milk must be the offender. Can an infant be hypersensitive to his own mother's milk? He can certainly react to drugs which his mother has been taking and which are excreted in her milk—as, for example, colic occurring in the infant when the mother has been taking cascara. It is less unlikely that cow's milk, with its non-human proteins, might provoke allergy, but the likelihood is decreased by the processing which the milk undergoes, and it is dried milk which most infants have nowadays in Great Britain. Nevertheless there is little doubt that an infant is occasionally seen who suffers from allergy to cow's milk. The diagnosis is not made by skin tests or by the existence of a leucopenia or by the finding of eosinophil leucocytes in the stools, but by careful clinical appraisal—namely, observing that the signs disappear when ingestion of milk ceases and regularly recur when milk feeds are again instituted. Such cases are very rare in Britain, but there may be a geographical variation in incidence. K. D. Bachman and S. C. Dees,[2] reporting observations from a paediatric allergy clinic in North Carolina, found that, of 172 infants under the age of 2 years who were referred to them because of suspected allergy, the diagnosis was confirmed in 109. Of these, 30% were sensitive to cow's milk, whereas in 403 well babies in the same age group they found an incidence of only 1%.

There will be very few infants in Britain for whom a milk-free diet is essential if they are to thrive. It is not necessary to go to such extremes of prophylaxis as omitting cow's milk from the diet of infants born of allergic parents, nor is it necessary to continue on a milk-free diet indefinitely, for the condition is, happily, only temporary. The important point is that allergy is a possible cause of colic or diarrhoea or vomiting in an infant, but that there are many more likely causes to be excluded first. Like neurosis, allergy is a diagnosis to be made by exclusion rather than the first to be considered, and the allergy clinic is likely to be, like the child guidance clinic—in all except the obvious cases—the last resort of the family doctor undertaking the care of the children.

[1] Glaser, J., *Allergy in Childhood*, 1956, Springfield, U.S.A.
[2] Bachman, Kay D., and Dees, Susan C., *Pediatrics*, 1957, **20**, 393.

PREVALENT RESPIRATORY DISEASES

The national statistics show that morbidity and mortality from respiratory diseases are at a higher level than they have been in recent years. We have therefore invited some general practitioners to report on the present appearance of these diseases in their practices, and their accounts appear in our Vital Statistics section this week (p. 111). A feature of them is the variety of distinct clinical syndromes noted in the at present ill-defined group of upper respiratory infections, and mention is also made of the epidemic vomiting that sometimes becomes prevalent in winter. The viruses causing febrile colds and chills still elude definition. As Dr. C. H. Andrewes, F.R.S., said last week-end,[1] "We are constantly coming up against the question of whether the common cold is due to a single agent or many." Dr. Andrewes discounted reports from the U.S.A. of an effective vaccine against the common cold, and, appealing for more volunteers to catch a cold at the Salisbury research unit, he added: "For some time now we have grown viruses of the group called adenoviruses. These cause a cold-like illness which is often feverish. But so far as the commonest kind of common cold is concerned we still find that we cannot cultivate a virus with regularity. Once we can do this with certainty we will be able to study its growth and behaviour in the test-tube." At the same time careful observations in general practice will help to define more clearly the various clinical types of febrile cold that may range from a mild sniff to a stinker.

[1] Statement issued jointly by Medical Research Council and Ministry of Health, January 4, 1958.

AN ANSWER TO SOME CRITICISMS OF CANCER EDUCATION

A SURVEY AMONG GENERAL PRACTITIONERS

BY

JOHN WAKEFIELD, B.A., M.R.S.H.
Executive Officer, Educational Project, Manchester Committee on Cancer

AND

R. L. DAVISON
Deputy Executive Officer, Educational Project, Manchester Committee on Cancer

In January, 1957, the Manchester Committee on Cancer completed the fifth year of an experiment in public education about cancer (Paterson *et al.*, 1954). Rejecting fear techniques, large public meetings, and the indiscriminate use of printed matter, the scheme emphasizes the hopeful outlook for those accessible cancers—breast, cervix uteri, and skin—which give rise to early symptoms easily recognized by the patient; and shuns such misleading general claims as "Cancer is curable." In those towns of South-East Lancashire and North Cheshire where the scheme has been conducted, over 700 lectures have been given to lay organizations and summarized in local newspapers. Publicity has therefore been maintained at a sufficiently high level of intensity for any ill effects to have forced themselves on the notice of general practitioners.

Object of the Survey

It was therefore decided to carry out a survey among doctors practising in the area to test the validity of the frequently voiced criticisms that cancer education would create cancerphobia among the public and add unnecessarily to the work of general practitioners. Some idea of the prevalence of this attitude to public education may be gained from the results of a survey carried out in 1953 by the British Empire Cancer Campaign (Horder, 1953). All general practitioners were asked if they considered that "the launching of a scheme of lay educational propaganda on cancer (by pamphlet, lectures, films, etc.) would be of assistance in securing the earlier diagnosis of cancer, and thereby improving the chances of a cure." Of the 24% who replied (5,053), more than half (2,683) were opposed to the idea of cancer education. But at that time few doctors had experienced the effects of a well-conceived cancer education scheme, and most were therefore being asked to forecast the probable outcome of an ill-defined situation. Doctors concerned in the present survey have, on the contrary, worked in an area subjected for five years to intensive propaganda of every suitable kind, and their views must carry correspondingly greater weight.

The objects of the survey were, firstly, to determine whether the cancerphobia anticipated by the critics of cancer education has materialized; and, secondly, to discover what general practitioners in the district think about the scheme. The survey was conducted by telephone, and doctors from all but 7% of the practices on the executive councils' lists for Ashton-under-Lyne, Bury, Heywood, Middleton, Oldham, Radcliffe, Rochdale, and Stalybridge were questioned. The number of questions was kept to a minimum; the final question left the doctor free to prolong or to close the conversation according to his own inclination and the time at his disposal.

Question 1: "Have the Committee's talks ever caused you any additional work—patients made uneasy by a lecture, who came to your surgery without observable symptoms?" *Answer:* Yes, 3; No, 105.

Of the three doctors who said "Yes," two said genuinely ill patients had come for advice at the same time. The third said the one patient in question was a confirmed hypochondriac and a regular visitor to his surgery with trivial complaints. These doctors accounted for three of eleven who said they were prepared to deal with the needlessly fearful patient if at the same time the patient with cancer was induced to come early.

Question 2: (*a*) "Have patients ever mentioned the talks to you?" *Answer:* Yes, 19; No, 89. (*b*) "To your knowledge have patients been induced by our publicity to consult you?" *Answer:* Yes, 9; No, 99. (*c*) "If patients came because of our publicity, were they justified by symptoms in doing so?" *Answer:* Yes, 6; No, 1; Some were, some were not, 2.

The answers to this question show a surprisingly high number of positive replies. It must be unusual for a patient to tell her doctor what induces her to seek advice, for it is undoubtedly unflattering to admit one has been impelled by others to take a course of action to which, by common consent, there is no sensible alternative. Nor is it likely that a doctor will concern himself with the reasons behind a visit from the really ill patient. But it is not unreasonable to expect him to probe more deeply when the visit of the cancer-conscious patient is not justified by symptoms, and he will remember the occasion long after he has forgotten the woman with simple mastitis, who, unknown to him, was prompted by the same talk to seek his advice.

It can be assumed, therefore, that the answers to Question 2 show an unfavourable picture of the propaganda's effects on the public; for more doctors will be aware of the few undesirable consequences than will know about its beneficial ones.

Question 3: "Have you any impression that in recent years women are more ready to seek advice at once for disorders of the breast and uterus?" *Answer:* Yes, 77; No, 21.

This question, formulated because of a doctor's observations early on in the survey, was put to 98 doctors. The answers of the 77 doctors who said "Yes" were qualified as follows:

Breast cases seem to come earlier. Little or no change with uterus	32
Uterus cases seem to come earlier. Little or no change with breast	10
There seems to be less delay with both sites	35

These are, of course, no more than subjective impressions. Some doctors admitted that their answers might well be influenced by recent distressing or encouraging experiences. Nevertheless a majority of practitioners in the area seem to think there exists a more matter-of-fact attitude towards symptoms which most women believe may have a serious explanation.

Question 4: "What is your opinion of this campaign? Do you think it has any value?" *Answer:* Entire approval, 97; Neutral, non-committal, "may be useful, and unlikely to be harmful," 10; Sceptical of value, 1; Harmful to public, none.

Doctors' Criticisms and Suggestions

This final question left doctors free to express their opinion of the value of the campaign and to offer suggestions for its improvement. In the first category are only those doctors who wholeheartedly endorsed the campaign: "Every doctor in Oldham knows about this and thoroughly supports it," "Who could possibly criticize this attempt to make people more aware of these things?" were typical comments.

Doctors who were reluctant to express an opinion without reflection, or who thought, "Your methods can't do much harm, and may possibly be valuable," form the second category. One objected to publicity about breast cancer, suggesting that to describe five-year survival after mastectomy

as a "cure" is to mislead the public. He agreed that there may be value in concentrating on other accessible sites —skin, cervix uteri, and bladder.

Only one doctor was thoroughly sceptical of the usefulness of the scheme. His criticisms were that even an informed lay public is "unable to exercise judgment," and that it is inaccurate to assess five-year survival for stage I cancer of the cervix uteri at any higher than 40%. He had no trouble with neuroses in his practice, because "my patients would be afraid to come to me without observable symptoms." He thought, however, the campaign could do little harm.

Not one doctor thought the scheme harmful. None had been caused any work he considered unnecessarily onerous.

Twelve doctors compared this project's cautious approach favourably with press, radio, and television publicity about cancer and health matters in general. There was strong and repeated criticism of sections of the press on the grounds that vague symptoms are presented as specific to a particular disease, that attitudes and emotions are not taken into account, and that the reader "is not in a position to ask questions." "Some of the women's magazines cause us more trouble than enough," summed up the general feeling. Eleven doctors volunteered the opinion that, in any case, they would not mind if the talks did bring one or two cases of phobia into the surgery. Some of these eleven thought the same net might also enclose the sensible patient with genuine symptoms; others thought the propaganda might be effective in bringing the already worried patient along, and looked upon the reassurance of this patient as part of their work.

Conclusion

Implicit in the comment of some doctors was a gratified surprise that any organization whose work might affect their patients should think their views important. It may be that the project's cordial acceptance by general practitioners derives from our first exploratory talks with B.M.A. Branches and other medical organizations, and from this subsequent inquiry. Possibly the large numbers who voted against the British Empire Cancer Campaign proposal in 1953 did so because the questionary did not specify what lines the propaganda would take: our experience is that once aims and methods are explained, and are seen to take account of possible dangers, the approval of a majority of the doctors in general practice is wholehearted.

The figures obtained in answer to question 3 depend entirely on doctors' impressions, voiced on the spur of the moment, and it would be wrong to attach too much importance to this part of the survey. But these results may indicate a real trend in public opinion about cancer in this region.

It is no doubt a just criticism that ill-conceived propaganda, wrongly delivered, may cause widespread cancerphobia; but the results obtained in this inquiry indicate that it is possible to saturate a given area with carefully devised publicity over a period of years with little or no undesirable consequence for either patient or doctor.

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MEDICAL NEW YEAR HONOURS

The names of the following members of the medical profession were included in the New Year Honours List published in the *London Gazette* on January 1.

Baronetcy

Sir HARRY PLATT, M.D., LL.D., M.S., F.R.C.S., Hon.F.A.C.S. Emeritus Professor of Orthopaedic Surgery in the University of Manchester. Lately President of the Royal College of Surgeons of England.

G.C.V.O.

Sir STEWART DUKE-ELDER, K.C.V.O., M.D., D.Sc., Ph.D., LL.D., F.R.C.S., F.R.C.S.Ed., F.A.C.S. Surgeon-Oculist to the Queen. Director of Research at the Institute of Ophthalmology. Ophthalmic Surgeon to St. George's and Moorfields Hospitals.

K.B.E. (Military Division)

PATRICK BRUNTON LEE POTTER, C.B.E., M.D., D.P.H., D.T.M.&H. Air Marshal. Director-General, R.A.F. Medical Services. Honorary Surgeon to the Queen.

ROBERT CYRIL MAY, C.B., O.B.E., *M.C.*, M.R.C.S., L.R.C.P. Surgeon Vice-Admiral. Honorary Surgeon to the Queen.

Knighthood

HENRY KENNETH COWAN, M.D., F.R.C.P.Ed., D.P.H. Chief Medical Officer to the Department of Health for Scotland. Honorary Physician to the Queen.

HERBERT RONALD ROBINSON GRIEVE, M.B., Ch.M., of Earlwood, New South Wales, Australia. For services to medicine.

HANS ADOLF KREBS, M.D., F.R.S. Whitley Professor of Biochemistry in the University of Oxford. Honorary Director of the Cell Metabolism Research Unit of the Medical Research Council.

WILLIAM BENTLEY PURCHASE, C.B.E., *M.C.*, M.B., D.P.H. Barrister-at-Law. One of H.M. Coroners for the County of London. Honorary Secretary, Coroners Society of England and Wales.

WILLIAM GEORGE DISMORE UPJOHN, O.B.E., M.D., M.S., F.R.C.S., F.R.A.C.S. Consulting Surgeon to the Royal Melbourne Hospital and the Children's Hospital, Melbourne, Australia. For services to surgery.

RALPH WHISHAW, C.B.E., M.B., Ch.M., F.R.C.P., F.R.A.C.P. Honorary Physician to Royal Hobart Hospital, Tasmania. For services to medicine.

C.B. (Military Division)

DOUGLAS BLUETT, O.B.E., M.B., B.Ch. Major-General, late R.A.M.C. Honorary Physician to the Queen.

FREDERICK ELVY LIPSCOMB, C.B.E., M.R.C.S., L.R.C.P., D.P.H., D.T.M.&H. Air Vice-Marshal, R.A.F. (ret.). Honorary Physician to the Queen.

ERIC THOMAS SUTHERLAND RUDD, C.B.E., M.B., B.Ch., F.R.C.S.Ed. Surgeon Rear-Admiral. Honorary Surgeon to the Queen.

C.M.G.

DONALD DIXON MCKENZIE, M.B., Ch.B., F.R.C.S., F.R.A.C.S. Senior Surgeon, Auckland Public Hospital, New Zealand.

C.B.E. (Military Division)

HUGH CUTHBERT SUTCLIFFE PIMBLETT, M.D., D.Obst.R.C.O.G., Group Captain, R.A.F.

C.B.E. (Civil Division)

ALEXANDER BROWN, M.B., Ch.B., F.R.C.P.Ed. Professor of Medicine and Head of the Department of Medicine, University College, Ibadan, Federation of Nigeria.

TREWAVAS PEARCE EDDY, M.R.C.S., L.R.C.P., D.P.H. Director of Medical Services, Sierra Leone.

GORDON LILICO, M.B., Ch.B., D.P.H. Lately Principal Medical Officer, Ministry of Health.

JOHN CAMPBELL MCINTYRE MATHESON, D.S.O., M.B., Ch.B. Principal Medical Officer, H.M. Prison, Brixton.

LAMBERT CHARLES ROGERS, V.R.D., M.D., M.Sc., F.R.C.S., F.R.C.S.Ed., F.R.A.C.S., F.A.C.S. Professor of Surgery in the University of Wales.

SEYMOUR COCHRANE SHANKS, M.D., F.R.C.P., F.F.R. Director, *X*-ray Diagnostic Department, University College Hospital. Consultant Adviser in Radiology to the Ministry of Health.

GEORGE HENDERSON STEVENSON, O.B.E., *M.C.*, M.B., Ch.B. F.R.C.S.Ed., F.R.F.P.S., M.R.C.P.Ed., D.P.H. Lately Chairman, Executive Committee, British Red Cross Society (Scottish Branch).

EDWIN ALFRED TRIM, O.B.E., M.D., D.T.M.&H. Director of Medical Services, Uganda.

O.B.E. (Military Division)

DAVID GEOFFREY DALGLIESH, M.R.C.S., L.R.C.P. Surgeon Lieutenant-Commander, R.N.

JOHN ERNSTING, M.B., B.S. Acting Squadron Leader, R.A.F.

CHARLES MCNEIL, M.B., B.Chir. Lieutenant-Colonel, R.A.M.C.

O.B.E. (Civil Division)

FRANK RICHARD ASHTON, M.B., Ch.B., D.T.M. For public services in Hong Kong.

CHARLES BOWESMAN, M.D., F.R.C.S.Ed., D.T.M.&H. Formerly Specialist (Surgery), Ministry of Health.

HAROLD CRAWFORD, M.B., B.S., F.R.A.C.S. Consulting Orthopaedic Surgeon, Brisbane Children's Hospital, Brisbane, Australia.

KATHERINE MARY HIRST, M.B., B.S., M.M.S.A., D.P.H. Senior Medical Officer, Ministry of Health.

THOMAS VICTOR HUMPHREYS, M.B., B.Ch. Lately First Secretary and Medical Officer at Her Majesty's Embassy in Moscow.

REUBEN JACOBSON, M.B., Ch.B. Director of Medical Services, Basutoland.

LEONARD ROSS MALLEN, M.B., B.S. Medical Practitioner in the Lower North District, South Australia.

TSOH-CHEN PAN, M.B., Ch.B. For social welfare services in North Borneo.

IVAN SAMUEL PARBOOSINGH, M.D. Senior Medical Officer, Jamaica.

JOHN PATRICK SEXTON, M.B., Ch.B., D.P.H., D.T.M.&H. Regional Senior Health Officer, Northern Region, Nigeria.

CLARENCE EDMUND SMITH, L.M.S., T.D.D. Assistant Director of Medical Services (Tuberculosis), Singapore.

JOSEPH STANLEY THOMAS, M.R.C.S., L.R.C.P., J.P. General Medical Practitioner, East Ham.

THOMAS JAMES RUSSELL WARREN, M.B., B.Ch., F.R.C.S.Ed., Hon.F.A.C.S. Director of the Samaritano Hospital, Sao Paulo, Brazil.

PHILIP RANDAL WOODHOUSE, D.S.O., *M.C.*, V.R.D., M.B., Ch.B. President of the New Zealand Catchment Boards' Association

M.B.E. (Civil Division)

GEORGE FRANCIS NICHOLAS ANDERSON, M.B., B.Ch. Senior Medical Officer with the Iraq Petroleum Company in Qatar.

ELIZABETH ABIMBOLA AWOLIYI, M.R.C.P.I. Lady Medical Officer, Federation of Nigeria.

ABRAHAM JOHANNES PETRUS COETZEE, M.R.C.S., L.R.C.P., D.T.M.&H. Chief Medical Officer, Rhokana Corporation, Northern Rhodesia.

GEORGE MILLAR EDINGTON, M.D., D.T.M.&H., D.C.P. Formerly Specialist Pathologist, Ministry of Health.

IRENE ELIZABETH BEATRICE IGHODARO, M.B., B.S. For social welfare services in the Western Region, Nigeria.

FRANK STANISLAUS LE MERLE, M.D. Lately Medical Practitioner at Basra, Iraq.

LATIMA KAMYA MUSOKE, D.M.S., D.C.H. Medical Officer, Uganda.

OLIVE HOPE ROBERTSON, M.B., Ch.B. President of the Federation of Women's Institutes of Southern Rhodesia.

JAMES SCOTT ROBINSON, M.R.C.S., L.R.C.P. District Medical Officer, Dominica, Windward Islands.

CYRIL AUGUSTUS WALLACE, M.B., B.Ch. Medical Officer, Tanganyika.

Reports of Societies

ROUND THE MEETINGS

Below are short accounts of recent meetings of the Heberden Society, the Royal Society of Tropical Medicine and Hygiene, and the Manchester Medical Society's Section of Anaesthetics. The subjects discussed included the arthritis which sometimes complicates ulcerative colitis, rheumatoid arthritis of the neck, and the use of phenylbutazone in rheumatic fever; animal reservoirs and filarial eradication campaigns; and the effect of carbon dioxide on relaxants.

HEBERDEN SOCIETY

The Heberden Society held its annual meeting on December 13 and 14. Dr. B. M. ANSELL and Dr. E. G. L. BYWATERS (London) had found that arthritis complicated 15% of all cases of definite ulcerative colitis seen at Hammersmith Hospital and the Canadian Red Cross Hospital, Taplow, during the last 10 years. They had studied thirty-seven such cases in detail. The knees and ankles were the joints most often involved, and, in contrast to rheumatoid arthritis, the hand and tarsal joints were much less frequently affected. There was a relatively high incidence of sacro-iliac involvement, and of particular value diagnostically was the swelling of the proximal and distal phalangeal joints of the toes. In most cases the arthritis took the form of a recurrent mild synovitis. Gross changes were found in only four cases, two of which had typical rheumatoid arthritis with nodule formation. In 25 of the 29 patients tested the Rose test was persistently negative. Eight of the 37 cases had erythema nodosum, and in one of them there was pericarditis also. These findings suggested that the arthritis was distinct from rheumatoid arthritis and due either to the factor that produced the gut lesion or secondary to the latter; or, if it was rheumatoid arthritis, that the clinical picture had undergone considerable modification as a result of the ulcerative colitis.

Rheumatoid Arthritis of the Neck

Dr. J. SHARP, Mr. D. W. PURSER, and Dr. J. S. LAWRENCE (Manchester) said that, if radiographs of the cervical spine of patients with rheumatoid arthritis, aged 55–64, were compared with those of controls of the same age, the features that seemed to characterize rheumatoid arthritis were narrowing of several intervertebral disks, particularly the upper two, with relatively little osteophytosis of the vertebral bodies and tendency to erosions rather than sclerosis of the adjacent plates; vertebral subluxation, particularly if occurring through narrowed disks or at more than one level; and erosion of apophysial joints. Using these criteria, they had examined 427 radiographs of the cervical spine from a random sample of this age group, reading the films without knowledge of the clinical, serological, or other radiological findings. They found the radiological changes in 6% of the males and in 7% of the females. Comparison with other criteria of rheumatoid arthritis suggested that where the spine was mainly or exclusively involved the condition might not be diagnosed as rheumatoid arthritis unless peripheral joints were also involved. This form of rheumatoid arthritis might be important in prevalence studies and it might account for some apparently "false" positives with the sheep cell agglutination test. Clinically, rheumatoid involvement of the cervical spine was serious because of the pain and also because of the danger of severe cord damage from the spine's mechanical instability.

Dr. J. BALL (Manchester) had made a post-mortem study of 20 cervical spines from typical cases of rheumatoid arthritis. Disk lesions were frequent, mainly in the postero-lateral and antero-lateral parts of the annulus but also along the disk-bone border in these regions. Serial sections indicated that the lesions were extensions of pannus arising in the roof or the anterior or posterior recesses of the neuro-central joint. In the affected area the annulus was replaced by granulation tissue. Atlanto-axial dislocation was found in three cases. Dislocation at the first, second, or third disk occurred in five; and in each instance there was associated erosion of the disk annulus posteriorly, anteriorly, or at both sites. Appreciable disk erosion was not necessarily accompanied by subluxation; occasionally this could be accounted for by ankylosis of the corresponding apophysial or neuro-central joint. In the single case where the dislocation had been severe enough to compress the cord there was some fixation above and below the level of dislocation, due mainly to ankylosis of apophysial joints. Similar disk lesions were not encountered in the cervical spines of 12 elderly control subjects without arthritis.

Heart in Rheumatoid Arthritis

Dr. B. CRUICKSHANK (Glasgow) said that a variety of non-specific cardiac lesions in patients suffering from rheumatoid disease had been described. The occurrence of rheumatoid granulomata in the heart was a well-recognized, though rare, finding, but most of the non-specific lesions were regarded as of rheumatic aetiology. In 100 patients with rheumatoid arthritis he had found rheumatoid granulomata in the mitral and aortic rings and cusps in five and in the

myocardium in one of them ; active rheumatic heart disease was seen once and healed rheumatic endocarditis in five patients, in two of whom no histological examination was made ; non-specific chronic endocarditis was seen in nine patients. Although the macroscopic appearances in these last patients suggested rheumatic endocarditis, microscopical examination failed to reveal characteristic lesions of that disease. In four of them there was active diffuse inflammation, with many of the features found in rheumatoid lesions elsewhere in the body, though no necrosis. These he thought were further examples of rheumatoid endocarditis. The other cardiac lesions encountered were myocarditis (10 patients), arteritis (20 patients), and pericarditis (15 patients), all of which were more frequent in patients admitted for the treatment of rheumatoid disease than in those admitted for treatment of intercurrent disease. Many of these patients had extensive involvement of tissues other than the joints. The incidence of rheumatic heart disease was no higher than in unselected necropsy cases, and he considered that rheumatic fever played no significant part in causing the cardiac lesions of rheumatoid disease. Many of the lesions were part of the rheumatoid process itself.

Phenylbutazone for Rheumatic Fever

Dr. G. WILL (Glasgow) described the results of treating 32 cases of acute rheumatic fever with phenylbutazone. All fulfilled the modified Duckett Jones criteria, and 17 of them were under the age of 17. In 21 it was their first known attack of rheumatic fever ; 11 cases had been initially treated unsuccessfully with aspirin. The maximum daily dosage of phenylbutazone was 600 mg. This was given for the first few days and was followed by 400 mg. daily for two weeks, and then 200 mg. daily for a further two weeks. In every case there was a rapid response to treatment. Joint pain and swelling were relieved within 24–48 hours and fever and tachycardia settled in three to five days. The sedimentation rate fell steadily to normal levels: in every case the E.S.R. had fallen to 15 mm. or below in one hour (Westergren) by the end of the fifth week of treatment. In two cases premature cessation of treatment was followed by relapse, with subsequent control on resuming treatment with phenylbutazone. There was only one serious toxic episode in the series—melaena. Mild epistaxis occurred in three cases.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

Control of Filariasis

On December 12 Dr. J. F. B. EDESON read a paper by Mr. R. H. WHARTON and himself on the experimental transmission of microfilariae from man to various animals. In 1953 a laboratory for the study of *Wuchereria malayi* was established at East Pahang in Malaya, as it was hoped to control or eradicate filariasis in that region. It was an essential prerequisite to discover whether there was any animal reservoir of infection which would prevent this. Microfilariae indistinguishable from those of *W. malayi* in man were known to occur in one species of Malayan monkey, but attempts to transmit the infection from man to monkey had hitherto failed. In their hands, however, transmission from man to various monkeys was accomplished, and a chance finding of *malayi*-like microfilariae in a dog subsequently led to the examination of other animals. Similar parasites were then found in other varieties of monkey, the slow loris, tigers, flat-headed cats, the Malay civet cat, the scaly ant-eater, and in domestic dogs and cats. Adult worms obtained from some of these animals were provisionally identified as *W. malayi* and others were described as a new species, *W. pahangi*. Further experiments resulted in the transmission of the infection to the slow loris, civet cat, and domestic cat, and strains of *W. malayi* were successively passaged through a monkey, a cat, a slow loris, and through a cat into a monkey and into other cats. Infections in cats appeared stable and had persisted for a year or more. The microfilariae in all the infected animals were indistinguishable from those of the human donors, developed similarly in vector mosquitoes, and shared the same periodicity. It seemed probable, therefore, that in Malaya animals formed a reservoir from which humans might acquire filariasis, although to date the infection had not been passed experimentally from animal back to man.

In the discussion, Professor J. C. C. BUCKLEY said that filarial infection in domestic cats constituted a complicating factor in any filarial control scheme. Professor R. M. GORDON saw no reason why an infection which was so readily transferable from man to cats should not be equally transferable from cats to man. Dr. F. HAWKING, however, found it surprising that filarial infections, usually host-specific, should be transmissible to a variety of animals, and doubted whether these animals could constitute a sufficient reservoir of infection to interfere with eradication campaigns. Sir PHILIP MANSON-BAHR said that in the light of Dr. Edeson's work morphology might henceforth cease to be the dominant factor in the classification of the *Wuchereria* group of filariae.

MANCHESTER MEDICAL SOCIETY

Carbon Dioxide and Relaxant Drugs

Dr. J. P. PAYNE (London) read a paper on the influence of carbon dioxide on the activity of relaxant drugs to the Section of Anaesthetics on November 21. Clinical experience had suggested that carbon dioxide modified the response, and to test the validity of this impression experiments were carried out using the anterior-tibialis–sciatic-nerve preparation in the intact cat. The relaxants tested were suxamethonium, decamethonium, gallamine, and tubocurarine. All four drugs did in fact modify the muscle response when carbon dioxide was inhaled. Carbon dioxide antagonized the neuromuscular blocking action of the depolarizing agents suxamethonium and decamethonium, and also the action of gallamine, but enhanced the effect of tubocurarine. The mechanism of these modifications was not clear, but two factors were possibly involved. First, it was known that the intensity and duration of action of a given dose of drug varied inversely with the fraction bound to protein and that alterations in plasma *p*H affected the ability of the plasma proteins to take up certain drugs. Secondly, recent work, particularly on barbiturates, had shown that the distribution of some drugs was altered in the presence of carbon dioxide. Further work was needed to determine whether the distribution of relaxant drugs was similarly influenced.

The design of operating theatres is the subject of the first *Hospital Building Bulletin* issued by the Ministry of Health and the Department of Health for Scotland. The bulletin is intended to assist those concerned with the design and planning of hospitals, and is based on a study of current practice in both the United Kingdom and abroad. The bulletin also gives some guidance on planning and cost. "The intention is to define the principles on which operating suites can be designed to function well and meet the requirements of those using them." It is stated that the issue of the bulletin in no way diminishes the need to provide architects with an adequate brief ; nor does it lessen the need for architects and engineers to consult and co-operate with local staffs of hospitals and others who are directly concerned with individual schemes. The primary concern is with new operating theatre blocks for either new or existing hospitals. It has not been found practicable to deal specifically with conversions of existing buildings, as each is a special case, but considerable information is provided for those designing conversion schemes. Further bulletins are being prepared on accommodation for nurses and on out-patient departments ; others will follow in due course. *Hospital Building Bulletin* No. 1 is obtainable from Her Majesty's Stationery Office, price 9s. net.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Familial Incidence of Addison's Disease

SIR,—The medical memorandum by Dr. P. H. Hewitt (*Journal*, December 28, 1957, p. 1530) concerning the occurrence of Addison's disease in siblings prompts me to record the following notes.

Miss A, aged 19, was sent to see me on April 29, 1948, complaining of symptoms thought to be neurotic. Her twin sister, B, in 1944 at the age of 14 developed symptoms of thyrotoxicosis, which were relieved after treatment with thiouracil for three months. She subsequently remained well until April 4, 1948, when she went to bed complaining of extreme fatigue and drowsiness. Restlessness and insomnia supervened and were associated with bouts of hiccups and occasional vomiting. In this state she was admitted to a local hospital, where she died suddenly in the night of April 14. A post-mortem examination was stated to have shown no cause of death. No detailed report on the state of the pituitary or adrenal glands was available.

Miss A, who was according to the mother a non-identical twin of B, had no illness until August, 1947, when she lost weight, with enlargement of the thyroid and exophthalmos. She was accordingly referred to the same physician who had treated B, who made the diagnosis of thyrotoxicosis. A was treated by rest in bed for six weeks and thiouracil for six months, after which she had recovered and was able to lead a fully active life until March, 1948, when she became tired and sleepy and again lost weight. Occasionally she would vomit after a meal. These symptoms persisted, and her weakness was such that she had to use a stick to support herself. She was seen again on April 6 by the physician who had previously treated her for thyrotoxicosis, from which he considered her now recovered. The diagnosis of anorexia nervosa was then suspected.

The patient's complaint when I saw her was of extreme weakness and of shortness of breath. On examination she was wasted with pigmentation like that of sunburn over the face and other parts exposed to light, and also a deep brown pigmentation of the nipples. There was slight exophthalmos and a small adenoma in the right lobe of the thyroid. The blood pressure was 70/40. The diagnosis of Addison's disease was suspected at this stage and she was admitted to Guy's Hospital under the care of Sir John Conybeare on May 5, where in the course of investigation she had an Addisonian crisis and died on May 22. The relevant post-mortem findings were confined to the endocrine glands. The adrenals to the naked eye were atrophied; microscopically both showed severe cortical atrophy, associated in one with local adenomatous hyperplasia. The thyroid contained a lobulated adenoma in the right lobe. The pituitary gland was of normal size, but contained a small, round tumour 3 mm. in diameter, which on section was a basophil adenoma. The thymus was appreciably enlarged, weighing 27 g.

It seems very probable that B's fatal illness was also Addison's disease. If so, there is a remarkable similarity between the life histories of these two twin sisters, both exhibiting thyrotoxicosis within the same period of three years, and both recovering from this, to succumb with symptoms of adrenal failure within six weeks of one another. It seems likely that the basophil adenoma of the pituitary is significant among the pathological findings: probably also the enlargement of the thymus. I am indebted to my colleagues of Guy's Hospital for permission to refer to their notes.—I am, etc.,

London, W.1. C. P. SYMONDS.

Hormone Therapy and Rheumatoid Arthritis

SIR,—I was delighted to read the letter from Dr. I. E. Bush (*Journal*, December 28, 1957, p. 1542) on the above subject. Contrary to implications in his letter I agree entirely with his view as to the essential difference between corticotropin therapy and the oral administration of cortisone or hydrocortisone. His suggestion that corticotropin therapy should be compared with hydrocortisone given by intramuscular injection I also agree with. In the early days of cortisone acetate therapy it was given entirely by intramuscular injection. Many abscesses resulted, especially when the cortisone was self-administered, whereas with self-administered corticotropin abscesses have been very rare. This complication kept us from studying intramuscularly administered corticosteroids until a few months ago, when we started again for just the reasons that Dr. Bush has put forward.—I am, etc.,

Sheffield, 11. HENRY F. WEST.

Surfeit of Medical Papers

SIR,—Next to exercising skill and care in treating patients, the obligation weighing most heavily on practising members of the medical profession is probably that of keeping one's knowledge up to date. Most physicians would probably accept this obligation willingly and devote the necessary time to it but for the feeling that they would be floundering in a morass. The Dean of Harvard (Dr. Sydney Burwell) has said, "Half of what you are now taught as medical students will in ten years have been shown to be wrong. And the trouble is, none of your teachers knows which half." Each year the bulk of medical publication increases, though it would appear that the significant content does not. It is difficult to believe that medicine is really developing so fast that knowledge has a useful half-life of only 10 years. Rather it would seem that the real advances are "lost" in ever-increasing masses of material published for reasons other than making new knowledge available to the profession. It is well known, and has come to be accepted, that professional advancement often depends on the number of papers one has published, so papers which even their authors do not consider significant are being submitted for publication. It is asking a great deal of medical editors to have them screen this material, but the fact that they are unable to do so satisfactorily is rapidly reducing medical publication to an absurdity—witness the accumulation of unread and even unopened journals. A look at the contents page of almost any current medical journal will discourage the practitioner who has perhaps only half an hour a day to devote to the literature. Refresher courses and conventions are expensive and unsatisfactory as alternatives to study of the literature, because there, too, self-advertisement is often a stronger motive in the speakers than is the altruistic desire to help one's colleagues.

One cannot ask practising physicians to sacrifice their leisure to the task of digesting all the published material. Those who have done this have paid the price of abdicating as members of their families and communities. That price is too high to pay for a familiarity with the current trash. No other profession has any problem approaching in severity this one which the medical profession faces.

Blame for the situation must rest firstly on selection boards for their policies, secondly on senior members of the profession for encouraging their juniors to conform to selection boards' requirements, and thirdly on medical editors who have not insisted on whatever help and guidance are necessary to screen out insignificant contributions, unconfirmed findings, inadequate statistics, unsubstantiated conclusions, and the host of other defects in the majority of published papers.

It will be asked by some, What other criteria can selection boards use when numerous candidates have apparently equivalent qualifications? It might help if authors of any verbal garbage were disqualified for a start. It might also help if selection boards could orientate themselves towards filling whatever vacancy may be in question. If a research worker is wanted, then important criteria would be ability to choose, plan, and carry out experiments and to draw justifiable conclusions therefrom. If a clinician is required then surely experience and judgment in the assessment of clinical states are more relevant considerations than the number of research projects which one has undertaken. Perhaps the best orientation to the problem could be achieved if it be acknowledged that medicine has now reached such a stage in its development that the careful

application of current knowledge to our patients' needs is more important to the general body of the profession than is research. Let us give at least as much credit for applying current knowledge to the needs of the present generation of patients as for pursuing knowledge which turns out to have been largely misconception.—I am, etc.,

Saskatoon, Canada. F. O. YOUNG.

Portable Stand in Domiciliary Midwifery

SIR,—Dr. Mervyn Goodman's excellent idea (*Journal*, December 21, 1957, p. 1493) for employing a photographic tripod as a lamp-stand suffers from only one inaccuracy. The British Standard tripod screw is not $\frac{5}{16}$-in. but $\frac{1}{4}$-in. Whitworth (20 threads/inch) (also the American standard) while the Continental fitting approximates very closely to $\frac{1}{4}$-in. Whitworth (16 threads/inch). There are no standard fittings employing a $\frac{5}{16}$-in. thread.

This is, incidentally, one of the few occasions when your admirable custom of giving metric equivalents breaks down—the British $\frac{5}{16}$-in. Whitworth (24 threads/inch) in no way corresponds either in pitch or thread form to a metric 5 mm. screw, which has approximately 30 threads/inch.—I am, etc.,

Manchester, 13. ROBERT OLLERENSHAW.

Aphthous Ulceration of Mouth

SIR,—I read your leading article on aphthous ulceration of the mouth (*Journal*, November 9, 1957, p. 1099) with interest, as I am myself, since my early days, a sufferer from this disease. I am now 47, and I cannot recollect a period of my life of more than a month in which my mouth has been completely free of any ulcer. The ulcers may be isolated or in a crop of two or three to five; sometimes they are very painful, sometimes less so. On some occasions especially if on the edge of the tongue, the ulcer is deep and inflamed; generally it is superficial. I cannot relate the ulceration to any special food, but some kinds of food can make things worse if ulceration is present. The ulcers generally come together in a crop, in all places of the mouth, also on the tonsils, but only in the latter case with high fever of 3-6 days' duration; the other mucosae have always been completely free. A new crop starts generally when I feel tired, especially if I have had to lose sleep. Local trauma, such as biting, gives origin in almost 100% of cases to a solitary ulcer; from this after a few days, other ulcers can occasionally develop, but not near to the first one. If I have a small ulcer, nuts, some kinds of cheese, or hard drinks will very often start off a new crop, but seldom if I am feeling perfectly well. As for therapy, I have tried almost everything; the only helpful substances have been benzocaine or lignocaine locally applied. No improvement whatsoever I found in vitamins, liver extracts, antibiotics, hydrocortisone, or prednisone.—I am, etc.,

Rome. G. SBARIGIA.

Giving Up Smoking

SIR,—There is evidence that a large number of patients would like to give up smoking in view of the recent considerable propaganda regarding carcinoma of the lung, but many of them lack the necessary will power. Smoking deterrents are advertised in the daily newspapers and would appear to depend on metallic salts which produce an unpleasant taste if smoking is continued. American work by Dorsey,[1] Wright and Littauer,[2] and Rapp and Olen[3] showed that lobeline was capable of relieving the withdrawal symptoms which occur when giving up smoking. Lobeline, however, has considerable side-effects, notably gastric distress, and it was found only to be of use when combined with antacid.

We conducted a trial designed to assess the usefulness of lobeline in relieving the withdrawal symptoms. Tablets were prepared as follows and could not be distinguished from one another. Batch 1: lobeline HCl 1 mg., sod. bicarb. 15 mg., gel alum. hydrox. sicc. 125 mg., together with 1/200 gr. (0.32 mg.) of copper sulphate in the sugar coating. Batch 2: similar but not containing lobeline. Batch 3: placebo (antacid only). Patients who wished to give up smoking were told to take 2 tablets every four hours up to a maximum of 8 tablets per day. The pills were to be retained in the mouth for a few seconds to allow the copper sulphate to have some effect. In all, 60 volunteers took part in the experiment and were seen 7 and 14 days after the start of the test. Results afterwards showed that: (1) 25% of the patients were successful in cutting out or drastically reducing their daily cigarette consumption, regardless of the type of tablet they were taking. (2) A little over 50% of the patients were smoking less towards the end of the second week than when they first started regardless of the type of tablet they were taking. (3) Less than 25% of patients failed to respond at all.

One must therefore conclude that there is no difference in the efficacy of lobeline, copper sulphate, or placebo as smoking deterrents. Supplies for the trial were kindly made available by British Schering, Ltd.—We are, etc.,

London. ROBERT A. MILEY, British Schering, Ltd.

Oxford. W. G. WHITE, Morris Motors, Ltd.

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Five Years of General Practice

SIR,—Dr. John Fry's article (*Journal*, December 21, 1957, p. 1453) is an excellent piece of work, and both from the point of view of the over-all planning of the Health Service and the teaching in our medical schools such studies are to be welcomed. I should like to make some comments, less in a spirit of criticism than in order to elucidate further a few of the difficulties inherent in a statistical investigation of this nature. As a general practitioner with a special interest in psychiatric problems my first query, on looking at Dr. Fry's figures, is the percentage given of the incidence of "psychoneuroses." The figure of 8.5% is so low in my experience and that of other workers that one has to infer very limited diagnostic criteria. Dr. Fry has not made it clear whether he has confined this category to the major neuroses (hysteria, phobias, and the obsessional states), or whether he includes all predominantly emotional problems, such as depressions, sexual difficulties, acute and chronic anxieties. Further, it is not clear from the article whether he has limited this category to those patients who give their neurotic symptoms as their reason for attendance, or where no organic disease is found.

Two weeks ago a young man consulted me about the progress of a burn on one hand. The lesion was very superficial, microscopically small, and a week old. While I was still thinking that this was a trivial reason for attendance, the young man, busily buttoning his overcoat, began: "By the way, doctor . . . ." and it emerged that he had quite a different reason for coming, which was connected with his marriage. This case illustrates that the patient's presenting symptom or illness may be insignificant in relation to the underlying problem for which he wants help. I do not think that statistics which place my patient solely into the category of, say, "injuries" would tell us anything very important about general practice. The reverse is also true, though probably not as frequent: a patient may complain of irritability and tiredness, and we find that he has, say, an anaemia.

In connexion with Dr. Fry's observations on sex differences one must bear in mind that the ratio of three to one does not tell us whether women are more often neurotic than men. There are many cultural factors which one has to take into account, and there is the impressive evidence of the attendance rates in our Child Guidance Clinics which show that far more boys are referred than girls, and again

one has to take into consideration such factors as the attitude of society towards aggression in children. One last comment. I think Dr. Fry is over-optimistic when he writes that it would be "of great comfort" to a patient to know that he will probably lose his migraine in old age. We could offer the same reassurance to all young women who complain of dysmenorrhoea or menorrhagia, but this would be poor consolation, and poor doctoring.

Dr. Fry would obviously agree that a detailed study of his practice cannot be held to be a random sample, because of geographical and social factors. I wonder whether he would also agree that it is further selected on the basis of the doctor's interests and personality, and his patients' expectations ?—I am, etc.,

Heaton Chapel, Stockport. ALFRED MODEL.

Abuse of E.C.T.

SIR,—Dr. H. Rassekh (*Journal*, December 21, 1957, p. 1493) restates some of the valid points, but I am in some doubt about his wishes. Any general or specialist practitioner is expected to treat illness logically—that is, by way of getting and assessing the relevant facts. Of course it is not always easy to do this, or, having done so, to act in the ideally best way in regard to them. Dr. Rassekh implies that we know what to do but don't bother to do it; or we don't know and "can be more precise in diagnosis." How ? Does he mean take longer histories; have longer periods of observation (in- or out-patient) ? Or do psychometric assessments on all, or do Funkenstein tests, or what have you ? Most cases of endogenous and similar depressive illness offer little diagnostic difficulty, but the vast range of mixed and atypical psychiatric states does not, in my experience, submit so readily to acute diagnosis calling for a specific mode of treatment; one selects the most likely of the best available.

Few would disagree about the magic of electroplexy in endogenous depression or about the surprise we sometimes feel when a patient responds to it in other hands after we had thought it unlikely to help, or indeed to be contra-indicated on psychopathological grounds. Intellectual or ethical laziness bringing off a coup ? Different facts ? Different assessment ? Different therapeutic approach ? Dr. Rassekh also mentions treatment of "even . . . cases of . . . cerebro-vascular disease," cerebral tumour, and disseminated sclerosis. But patients so suffering also do have depressive illness, and it is something of an experience to see the amazed and amazing relief of patient (and relatives) at the prospect provided by electroplexy of tolerable existence. In what way, then, is electroplexy more abused than any other therapeutic agent in medicine and surgery ? Reasonable study of the patient and his circumstances should not equate with inaction nor lead to inappropriate action, since there are few, if any, contraindications for electroplexy with modern techniques and we should keep our minds on the pros rather than the cons. Perhaps I should add that, in the group in which I have the privilege of working, we are fussy about the indications for therapy—but not afraid of them.—I am, etc.,

London, W.1. L. ROSE.

Dislocation of Jaw

SIR,—The amusing cases of recurrent dislocation of the jaw described by Dr. Ivor W. Hockley (*Journal*, December 28, 1957, p. 1543) fall chiefly into the category of subluxation of the temporo-mandibular articulation, probably associated with weak ligaments supporting the joint. In view of this, it is thought expedient to point out a risk to the operator when the reduction is carried out by the usual method of inserting the thumbs in the region of the angle between the body and ascending rami of the mandible, depressing with the thumbs and elevating the chin with the fingers. In cases of young people with good muscle tone, tight ligaments, a pronounced eminentia articularis, and posterior opposed molar teeth *in situ*, as in the case of a boxer, or a dislocation by use of a gag during anaesthesia, the reduction of such cases may take place suddenly and with considerable force, crushing the operator's thumbs between the patient's back teeth. Metal thumb-shields have been designed to prevent this, but a piece of wood suitably shaped, a stout pencil, or any object of similar shape may be more sensibly employed as a fulcrum.—I am, etc.,

Liverpool, 6. G. ELLENBOGEN.

Erythrocyte Sedimentation Rate

SIR,—In their paper on the causes of anomalous results in the erythrocyte sedimentation rate (*Journal*, December 14, 1957, p. 1405) Drs. F. T. Shannon and E. G. L. Bywaters make scant reference to Continental work on the subject. They also do not discuss as a cause of these irregularities the prolongation of the aggregation phase of sedimentation. Following the preliminary report by Goldberg, Glynn, and Bywaters,[1] I reported the results of my own findings.[2 3] I showed that these anomalies occur when a solid anticoagulant is used, and that they were due to a prolongation of the aggregation phase of sedimentation. As this phase was observed to end suddenly with the formation of large rouleaux aggregates and followed by rapid sedimentation, I considered that it was due to a metastable state and suggested that the condition might be a hysteresis phenomenon. This phenomenon appears to have been first observed by Lundgren[4] when studying erythrocyte sedimentation in hirudinized blood. Mårtensson and Hansen[5] have made an exhaustive study of the subject which they have termed the "reversed E.S.R." They showed that the length and bore of the Wintrobe tube is inadequate for the sedimentation of undiluted blood, and that for unimpeded sedimentation the tube bore has to be at least 5 mm. and the length greater than 200 mm. I recently reviewed the literature on these E.S.R. discrepancies.[6]

During my experiments with the sedimentation of heparinized and also with oxalated blood, I frequently observed a very prolonged aggregation phase. When aggregation did occur, sedimentation was very rapid. I have also observed a similar phenomenon in Wintrobe tubes. Although I agree with Drs. Shannon and Bywaters that, when both the packed cell volume and viscosity of the blood are high, the fall of the large red cell rouleaux aggregates will be impeded due to the increased amount of plasma that has to be displaced, I consider that this cannot be the sole explanation for these anomalously low E.S.R. readings, for such an explanation envisages that aggregation has already occurred.—I am, etc.,

Enfield, Middlesex. McD. DUXBURY.

REFERENCES

1 Goldberg, S., Glynn, L. E., and Bywaters, E. G. L., *Brit. med. J.*, 1952, **1**, 202.
2 Duxbury, McD., ibid., 1953, **1**, 1050.
3 —— *Acta med. scand.*, 1954, **150**, 263.
4 Lundgren, R., ibid., 1927, **67**, 63.
5 Mårtensson, E. H., and Hansen, H. A., ibid., 1953, **146**, 164.
6 Duxbury, McD., *Lancet*, 1957, **1**, 734.

Infants' Feeding-bottles

SIR,—Reading Dr. P. M. Fleury's letter (*Journal*, December 14, 1957, p. 1438) one assumes that she has fed only but one baby, and her condemnation of the boat-shaped bottle strengthens the assumption. She is quite right in her remarks concerning the size of the holes in teats, and many a feeding problem attending paediatric out-patient clinics has been cured by making the hole bigger. There are many "sloppy" feeders, however, in which this is insufficient, and the vacuum caused in the Soxhlet-type bottle continues to cause excessive air-swallowing. In these infants the boat-shaped bottle is almost invariably the answer, and even at times the valve must be taken off to overcome the problem.

I cannot argue about the ease with which the two types of bottle can be cleaned. My own three children were fed as Nature intended, and, although I have bottle-fed many babies, I have not undertaken the cleaning process myself. Our ward sisters assure me, however, that the boat-shaped bottles cause little difficulty in this respect, and in fact they

are easier to clean than Soxhlet bottles by virtue of the fact that they can be flushed right through. The declining popularity of the boat-shaped bottle seems to be causing an ever-increasing number of feeding problems. This decline is probably due largely to the fact that boat-shaped bottles are not made in heat-resistant glass.—I am, etc.,

Hull. MAURICE G. PHILPOTT.

Testing for Occult Blood in Faeces

SIR,—In his letter (*Journal*, December 21, 1957, p. 1488) Dr. A. G. Ogilvie asks for experiences of the *o*-tolidine method[1] for occult blood in faeces. We have used a slide modification for three years, and have found it entirely satisfactory, and suitable for ward tests, though perhaps less so for the general practitioner. We use a reagent composed of: 4% *o*-tolidine in ethanol, 2 ml.; glacial acetic acid, 2 ml.; distilled water, 2 ml. This is kept in a bottle fitted with a teat dropper, and is stable for many weeks in the refrigerator, and at least a fortnight at room temperature, though the colour may darken with time. To a smear of faeces on a siliconized cavity tile is added one drop of 20 vol. hydrogen peroxide, then one drop of the *o*-tolidine reagent. A blue or blue-green colour developing within 30 seconds is regarded as positive. We would stress that, in order to prevent doubtful results caused by atmospheric oxidation at the "creeping" edge of the drop, it is important that the tile should be treated with a silicone compound (e.g., "repelcote").—We are, etc.,

J. KOHN.
T. O'KELLY.

London, S.W.15.

REFERENCE

[1] Kohn, J., and O'Kelly, T., *J. clin. Path.*, 1955, **8**, 249.

Nitrous Oxide Bypasses

SIR,—There are still numbers of anaesthetic machines in use which have a bypass providing a rapid flow of nitrous oxide as well as one for emergency oxygen. The two controls are alike, though at opposite ends of the row of flowmeters. It can easily happen in the stress of an emergency that the wrong bypass is opened when it is intended to inflate a patient's lungs with oxygen. At least one fatality has been caused in this way. I suggest that lives may be saved if every anaesthetist who uses a machine that has a nitrous oxide bypass takes steps to have it removed.—I am, etc.,

Cambridge. H. R. YOUNGMAN.

Mongolism in a Twin

SIR,—I have been very interested to read the report of Dr. J. V. Morris on this subject (*Journal*, November 2, 1957, p. 1038) and the ensuing correspondence. As it appears to be a relatively rare occurrence I should like to report a case which has become known to me in the course of my duties as a school medical officer.

The child, now almost 9 years old, is one of twin girls who were the product of their mother's twelfth and last pregnancy. Of the mother's twelve pregnancies between 1923 and 1949 seven ended in the birth of a single normal infant at term, three ended as miscarriages at from two to three months, one immediately preceding the twin birth under discussion by one year and nine months, terminated as a single stillbirth in the eighth month, and the last twin pregnancy ended in the birth of living females at an estimated thirty-six weeks. During this last pregnancy the mother's age was 43 years and her health was good apart from an iron-deficiency anaemia which was treated with "fersolate." Blood group A, Rhesus positive, Kahn negative. The birth was uneventful; the mongol child weighed 5 lb. 2 oz. (2.32 kg.), and the other weighed 5 lb. 10 oz. (2.55 kg.).

In addition to being a typical mongol this child has a well-marked acyanotic congenital heart lesion and a convergent squint. Her intelligence quotient has been estimated as 36 on the Terman–Merrill revision of the Stanford–Binet scale. She has been ascertained as being ineducable and has been reported as such to the local authority under Section 56 of the Education (Scotland) Act of 1946. The twin sister is a normal child and attends at an ordinary school. The family is a "problem family" with apparently limited intelligence in both parents. There is no consanguinity. One of the mother's sisters has had twins, and this is the only other plural birth known on either side of the family. No other mongol is known of on either side.—I am, etc.,

Bridge of Allan, Stirlingshire. ROBERT G. MURRAY.

Casualty Department Attendance

SIR,—May I briefly reply to some of the points in Dr. John C. Pollard's letter (*Journal*, December 21, 1957, p. 1489) about my report on casualty department attendances? I could not agree more about the need for a positive approach to the mildly neurotic patients who complain of symptoms for which no organic cause is found. Indeed, I was prompted to write the paper partly by my growing realization that my student training had left me without any guidance on how to deal with one-quarter of my patients. But Dr. Pollard implies that many of these patients only wanted to be reassured that they were well. I wish he were right; for then there would be little difficulty in dealing with these people.

What happened to the 27% for whom nothing was to be found in the *National Formulary*? I should like to hazard a guess. Most of them went away a little less complaining for a while. As long as life was not too hard on them, they went about their business; and when the next period of stress and strain came upon them they joined another doctor's queue. These people are not incapacitated by their neurotic symptoms. They carry on; it is only a niggling ache that afflicts their spirit. And there are hordes of them. We must remember these facts in planning a "positive" approach. I am sure the place for these patients is not on the psychiatrist's couch but in the surgery of their doctor; a doctor who has the time and the inclination to listen, to think, to advise on what are so often not medical but social or personal problems—but, above all, to listen.—I am, etc.,

Wroughton, Wilts. P. MESTITZ.

Perineal Toilet

SIR,—With reference to the paper by Drs. R. T. Martin and H. E. Reiss on vulval and perineal toilet in the puerperium (*Journal*, September 21, 1957, p. 670), I handed the article, without comment, to the sister in charge of the maternity annexe here. Her remarks were brief: "Sounds as though we are back to the old Maoris—down to the river to bathe." She is of Maori descent.—I am, etc.,

South Taranaki, New Zealand. E. P. HOUGHTON.

Thyroid Association

SIR,—The Fourth International Goiter Conference is to be held in Britain in 1960, and the American Goiter Association, which usually holds its annual meeting in one of the cities of the U.S.A., is on this occasion holding its annual meeting in London in conjunction with the International Conference. The London arrangements for these meetings are being made by a committee of the London "Thyroid Club."

These developments have raised the question of whether there should be formed a "Thyroid Association of Great Britain" or "of Europe," which should probably be linked in some way to the Society for Endocrinology and the Section of Endocrinology in the Royal Society of Medicine. If those who feel that some such association should be formed would notify the undersigned, the amount of support for this idea could be ascertained. If it then seems desirable a preliminary meeting will be arranged, possibly in association with the national joint meeting of the Society for Endocrinology and the Section of Endocrinology in the Royal Society of Medicine.—We are, etc.,

London, W.12. RUSSELL FRASER.
SELWYN TAYLOR.
Glasgow, W.1. E. J. WAYNE.

Obituary

Sir ERNEST KENNAWAY, D.M., D.Sc., F.R.C.P. F.R.S.

Sir Ernest Kennaway, who died at St. Bartholomew's Hospital, in his sleep, on January 1, devoted his whole career to medical research. He was 76 years of age. His work over a period of 50 years in the laboratories of Guy's, St. Thomas's, St. Bartholomew's, and the Middlesex Hospitals, and at the Lister Institute and the Chester Beatty Institute, of which he was formerly director, was regarded by all who had the training and skill to understand its value as of the very highest worth. His early research was concerned with many aspects of clinical pathology. Later, as the study of cancer and its genesis engrossed him, he sometimes took a wider view and would explore, for example, industrial and sociological aspects of cancer. Personally he was well equipped as a research scientist. He had the patient mind, the objectivity, the restrained enthusiasm of the true researcher. Alike at the bench, observing, selecting, and assessing significance, and afterwards at the desk or dais expounding the results of his observations in clear and effective writing or speech, he was a master workman. He never made exaggerated claims, he was content to weigh and count and measure, believing as he did that the truth was gradually elicited by the careful accumulation and correlation of data. His natural diffidence in public disguised to some extent the brilliance of his mind and his achievements, but in any ultimate solution of the cancer problem Kennaway's work will rank high.

[*Walter Stoneman*

The son of Laurence James Kennaway, of Exeter, and bearing a family name well known in Devon, Ernest Laurence Kennaway was born on May 23, 1881. He went to New College, Oxford, with an open scholarship in natural science, and took a first-class in the final honours school of natural science in 1903. Later he was to become an honorary fellow of New College. Having won a university scholarship to the Middlesex Hospital, he graduated B.M., B.Ch. in 1907, proceeding to the D.M. in 1911. During his whole career as a student and afterwards—though he never really ceased to be a student—he showed unusual capacity. In any competition within his range, the prize always seemed to fall to him. After short periods of work at the Lister Institute and at University College, Kennaway was appointed demonstrator of physiology at St. Thomas's Hospital in 1908; in 1909 he was Hulme research student at Brasenose College, Oxford; from 1909 to 1914 he was demonstrator of physiology at Guy's Hospital; in 1911 he was awarded a Radcliffe travelling fellowship by the University of Oxford and studied at Heidelberg and at Munich. During the first world war he worked as a chemical pathologist at the Middlesex Hospital on such military problems as the sterilization of drinking-water and on the antiseptic treatment of wounds. In 1915 he obtained the D.Sc. of London University. He first joined the staff of the Royal Cancer Hospital (now the Royal Marsden Hospital) as physiological chemist in 1921; in 1928 he was awarded the William Julius Mickle fellowship of the University of London; and he was appointed to the chair of experimental pathology, tenable at the Royal Cancer Hospital, where he was also director of the Research Institute. He retired from the staff of the Royal Cancer Hospital, to become professor emeritus, in 1946.

Kennaway's early work covered a wide field, but as time went on he concentrated more and more upon the investigation of cancer. As early as 1922 in this *Journal* he was writing on the experimental production of cancer by arsenic, and again a year or two later on cancer-producing substances in general. Some work of his, published in the *Journal of Industrial Hygiene* in 1925 and 1926, discussed the anatomical distribution of occupational cancers and the incidence of cancer of the bladder and prostate in certain occupations. In particular, he made a close study of cancer-producing tars and tar fractions, and was one of the team of workers who ultimately identified 3:4-benzpyrene as a carcinogenic compound in coal-tar. In 1939, he and his colleagues, W. V. Mayneord, I. Hieger, J. W. Cook, and C. L. Hewett, shared the first award of the Anna Fuller Memorial Prize "in recognition of their notable accomplishments in the fields of cancer research, specifically for the isolation and synthesis of cancer-producing hydrocarbons from coal-tar, the identification by fluorescence spectroscopy, and for the study of the biological effects of these substances."

Kennaway's studies of cancer were not confined to work of a chemical nature. He wrote on the effect of circumcision in relation to the incubation period of cancer of the male generative organs, and more recently he contributed to the controversy on the causation of lung cancer. In 1949 he was writing on the increase of deaths attributed to cancer of the lung. He investigated the arsenic content of tobacco and tobacco smoke and also the arsenic in suspended matter in town air. With his wife, Nina Marion, daughter of the late William Derry, of Edgbaston, whom he married in 1920, he collaborated in several papers on the incidence of cancer of the lung and of the larynx and pharynx. In recent years he had discussed in several papers published in this *Journal* outstanding problems in the study of cancer. Kennaway was elected F.R.S. in 1934, F.R.C.P. in 1937, and was awarded a Royal Medal of the Royal Society in 1941.

His many-sided and original work made him an outstanding figure in the British Empire Cancer Campaign, which recognized his services by the award of the Garton prize. His work was also highly esteemed in the United States, and was recorded in many of the specialist journals there. He was made an honorary fellow of the New York Academy of Medicine and an honorary member of the American Association for Cancer Research. In 1930 he had been the recipient of the Walker prize of the Royal College of Surgeons, awarded for the best work in advancing the knowledge of the pathology and therapeutics of cancer during the preceding five years. In 1937 he received the Baly medal and in 1950 the Osler memorial medal, which is awarded once every five years to the Oxford medical graduate who has made the most valuable contribution to the science, art, or literature of medicine. In 1947 he received the honour of knighthood, and he was made an honorary fellow of the Royal Society of Medicine in 1952.

After leaving the Royal Cancer Hospital Sir Ernest Kennaway was asked to continue his researches at St. Bartholomew's Hospital, and although his health had been poor for several years he was at work almost up to the time of his death. Only eighteen months ago he visited the U.S.A. and gave the Richardson lecture at the Massachusetts General Hospital, and despite his age and ill-health his keenly observant eye was, as usual, taking in significant and interesting facts about America (*B.M.J.*, 1956, **2**, 933). The last of his many contributions to this *Journal* was just before Christmas (December 21, 1957, p. 1485), when he had some very apt things to say about nursing from the patient's point of view. Facts were what mattered to him, and he was an out-and-out rationalist. In 1953 he ventured into the wider realms of literature and published a small

volume—*Some Religious Illusions in Art, Literature, and Experience*—in which he attacked some common beliefs. But he never allowed his agnosticism to cast a shadow over his social relationships with his fellows, and he will be mourned by a large company of friends extending far beyond the ranks of those engaged in scientific research.

We are indebted to Professor ALEXANDER HADDOW for the following appreciation: Kennaway was the doyen of cancer research in this country, and as such, and as a leader, received international acclaim. Yet not all his scientific life was spent in the cancer field, and we must not forget a whole series of papers, from about 1910 to 1920, which revealed the breadth of his knowledge and interests in chemistry, physiology, and pathology, and which gave a taste of things to come. Certainly, however, it is upon his massive achievements in the sphere of malignant disease—and especially in that of chemical carcinogenesis—that his name and fame are based and will endure. Curiously, an early paper in this phase, on the experimental production of cancer by arsenic (with A. Leitch, *Brit. med. J.*, 1922, **2**, 1107), was one on which he set much less store in later years. But this subject continued to exercise him, and a further contribution, on the effect of arsenic upon some oxidation-reduction systems (with G. Barry and E. Bunbury, *Biochem. J.*, 1928, **22**, 1102), is still much consulted, and may indeed have greater significance than was appreciated at that time.

In the early 'twenties great efforts were under way to elucidate the nature of the cancer-producing agent in tar and pitch, following the successful production of undoubted cancer through application of coal-tar to the rabbit skin by Yamagiwa and Ichikawa (1915) and in the mouse by Tsutsui (1918). Between 1921 and 1926, Bloch in Zurich had found that the active substance was concentrated in the higher boiling fractions as a neutral compound, free from nitrogen, arsenic, or sulphur, capable of forming a stable complex with picric acid, and probably belonging to the class of cyclic hydrocarbons. In 1924–5 Kennaway succeeded in producing carcinogenic tars by the pyrolysis of petroleum, skin, hair, yeast, and cholesterol, and by leading acetylene and isoprene with hydrogen through heated tubes. The tars obtained at successively higher temperatures (450–1,250° C.) showed an ascending order of potency; and these results could be explained by assuming that acetylene was a common decomposition product, that the carcinogenic material was built up from it, and hence that the carcinogenic material was actually formed from acetylene. There gradually emerged the strong general conclusion that the carcinogenic agent was indeed a complex hydrocarbon of aromatic type.

In all this work Kennaway ever acknowledged the value of Berthelot's classical paper of 1866, describing for the first time the production from acetylene of these very kinds of molecule.

We are fortunate indeed that Kennaway himself left his own characteristic account of these and later developments (*Brit. med. J.*, 1955, **2**, 749), setting forth their history, and making clear the part played by those in his school at the Cancer Hospital—W. V. Mayneord's examination of the fluorescence spectra of the carcinogenic tars, and the discovery of their special qualities (1927); the development by I. Hieger of this vital clue; the discovery that 1:2-benzanthracene gave a spectrum similar to that of the carcinogenic mixtures; J. W. Cook's studies of the benzanthracene homologues; and, by no means last, Kennaway's own indebtedness to the help of his assistant, Frank Goulden. About this time Erich Clar had just published methods for the synthesis of certain benzanthracene hydrocarbons. These compounds were tested for carcinogenic activity by Kennaway and Hieger (1929–30), who soon observed positive results with 1:2:5:6-dibenzanthracene: this was the first pure compound manifesting pronounced carcinogenic properties, and one cannot forget the satisfaction and modest pride which Kennaway obtained from the fact. The fluorescence spectrum—in Kennaway's words "the single thread that led all through this labyrinth"—was also used by Hieger in the concentration of the agent from coal-tar pitch, culminating in the isolation of a hydrocarbon which showed the characteristic spectrum and which proved to be strongly carcinogenic (1933). Its properties suggested one of the two benzpyrenes, and these were synthesized by J. W. Cook and C. L. Hewett, who were then able to prove the identity of one of the compounds (3:4-benzpyrene), and the substance from pitch. All these, and many other results, which Kennaway alone inspired, are embodied in numerous papers (many of them classics), in the *British Medical Journal*, the *Journal of Industrial Hygiene*, the *Journal of Pathology and Bacteriology*, the *Biochemical Journal*, the *Journal of Hygiene*, the *American Journal of Cancer*, the *Yale Journal of Biology and Medicine*, *Nature*, *Cancer Research*, the *British Journal of Cancer*, and, most notably, in a celebrated series on the production of cancer by pure hydrocarbons, which appeared in the *Proceedings of the Royal Society* between 1932 and 1942.

These were thrilling days, not least from the recognition of a possibility that such compounds might play a part in the causation of "spontaneous" cancer. This followed the advances in sterol formulation due to Rosenheim and King in 1932, showing that many such naturally occurring compounds have somewhat similar condensed polycyclic systems. Also, J. W. Cook had drawn attention to evidence suggestive of an inherent tendency for certain sterol molecules to pass into carcinogenic derivatives. There is as yet no proof that changes of this kind take place, or do not take place, *in vivo*. Yet the possibility was one which continued to intrigue Kennaway, and led him to confirm an observation of Ghiron, that the bile-acid deoxycholic acid is capable of producing connective-tissue tumours in mice. This result is of particular interest, since Wieland and Schlichting had already prepared from deoxycholic acid the hydrocarbon dehydronorcholene—a hydrogenated derivative of 1:2-benzanthracene—from which in turn both Wieland and Dane, and Cook and Haslewood (in 1933) obtained, by dehydrogenation with selenium, the fully aromatic and powerfully carcinogenic hydrocarbon methylcholanthrene.

What undoubtedly emerged from almost thirty years of brilliant work was a satisfying and indeed beautiful correlation between chemical constitution and biological action, whereby the carcinogenic sub-classes—phenanthrenes, dibenzphenanthrenes, chrysenes, pyrenes, and benzanthracenes—could clearly be related to the parent phenanthrene, in a system suggesting dependence upon certain optimal features of molecular size, shape, and substitution. But we must not minimize another result—namely, the profound practical influence which was exerted upon the whole of cancer research, and indeed biology widely, from the mere availability of these potent carcinogens, so rendering possible, and catalysing, numberless other investigations, and additions to knowledge, which could not have been attained without them.

No imagination is needed to see how this career demanded a patient sense of purpose and intensive application over so many years. Yet even within the cancer field Kennaway showed broad interest and curiosity, and, in addition to his many preoccupations in the laboratory and in administration, he also found time to write papers on a great diversity of aspects, including occupational cancers, the serum proteins in malignant disease, the nitroprusside reaction in normal tissues and in tumours, the incidence of carcinoma of the lung and larynx, the carcinogenicity of azo-naphthalenes, cancer of the liver in the African and American negro, and the social distribution of cancer of the scrotum.

In a prophetic sentence written as long ago as 1851, *(Traité pratique des maladies cancéreuses)*, Lebert believed that the discovery of cancer-producing agents could only come about through the joint efforts of one accomplished in the anatomy and pathology of cancer and a chemist versed in science. This conjunction was certainly reached when Kennaway joined forces with J. W. Cook. But in many ways Kennaway possessed all the necessary qualities in his own being—in his intellectual aptitudes, his chemical sympathy and knowledge, and in his unrivalled skill in

applying them to physiology and pathology. Apart from his modern scientific bent, he was also a true naturalist, believing greatly in field work and epidemiology. I recall the story of his triumphant return from an expedition to a dyestuffs factory (many years ago, to study the role of aromatic amines in producing bladder cancer in man), his clothing and skin liberally bespattered with dyestuffs and intermediates, as the visual evidence of how industrial contamination occurred in those days.

Kennaway's standards of evidence were rigorous and severe, to the point of austerity. His experimental methods were simple, practical, and decisive, and a delight to watch in execution. He was much less interested in hypotheses, explanations, and mechanisms, and, although his own work had lain almost entirely in the chemistry of carcinogenesis, he remained completely open and free to accept any other mechanism or interpretation—viral or otherwise—provided only that the facts were ascertained, and not an instant before. Added to all these gifts, he was a master of scientific expression and of English construction. He especially disliked the use of hypothetical or presumptive words or phrases, on the simple ground that so many things which "should" take place in this world in fact don't.

We have lost a great seeker and searcher, a great discoverer and scientific worthy. Amongst his personal attributes and qualities two things prevailed. First, his profound agnosticism. At the same time, although a supreme sceptic, he worshipped the unvarnished fact when once it had become established. Secondly, his superb and stalwart fortitude, which enabled him to conquer the trials and master the vicissitudes not only of illness but of grievous accident, and to continue his researches long after his official retirement and almost to the day of his death. Of course he had many other interests—including an attachment to the music of Bach—and many human concerns which he did not parade and which, contrariwise, he often tried to conceal.

No appreciation could be complete which failed to refer to a factor at all times apparent to those around him—the part played by Lady Kennaway in every aspect of his life and work. We mourn with her, and share her pride, and will hold him in affectionate and ever-grateful remembrance.

Dr. E. F. SCOWEN writes: The first and last impression of Kennaway was the indefinable quality of greatness. Neither from achievements, though these were his in abundance, nor from personality alone did this quality emanate. Initial acquaintance revealed an apparent austerity, a dogged perseverance, an unswayable purpose, and an insatiable curiosity, but all these tempered with humility. The great human qualities beneath this rugged exterior were shuttered from those not privileged to know him well, both by natural diffidence and the screen of his physical disability.

He was a methodical, accurate, and infinitely painstaking collector of facts, a masterly designer of experiment, and a scrupulous recorder. To all this he brought a truly remarkable scientific judgment, at once finely balanced and imaginative. From him never the extravagant claim the facts could not prove, yet he could admire the complexities of nature, whose mysteries he strove to unravel. His energy and industry seemed inexhaustible. His indomitable will allowed no concession for his physical handicap, and respite for relief was but a preparation for further effort. Small wonder his achievements were so great and so many. Much of his life was devoted to cancer research, but his interests remained wide, and to all that was new he was ever acutely and shrewdly perceptive. The breadth of his knowledge in diverse subjects was astonishing, as many ill-informed discovered to their chagrin. He never seemed to forget anything.

He was a great man of science, yet was he also but a man. Iron mental discipline could not always control the latent tempestuous nature, nor was his personal judgment always punctiliously dispassionate. Not for him gentle and ephemeral emotions; he liked and disliked vehemently, enduringly, and with equal intensity: vulnerable to paranoid tendencies, he sought not defence, aggression his true solace. He was implacable in hostility, yet loyal to a fault, warm, generous, and human in friendship, capable of remarkable devotion to those he loved, and of an astonishing and childlike faith in those he trusted, but totally unable to accept any mystical approach to ultimate truth. Through all his life there emerges one dominant theme, a perpetual struggle for truth. To this end he was both infinitely patient and fanatically energetic, for a truth was capable of proof. Time was precious. To one man is given such a short span to seek the truth. How typical of the man was our first meeting many years ago for a discussion of experimental proof and our last on the day of his death for advice and instruction on a new experiment. All this, whilst through many years seeking and accepting without question medical treatment, often, alas, of necessity highly empirical.

W. J. FENTON, M.D., F.R.C.P.

Dr. W. J. Fenton, consulting physician to Charing Cross and Brompton hospitals, died at Brompton Hospital on December 24, 1957, the 89th anniversary of his birth.

William James Fenton was born at Aston Manor, Warwickshire, on December 24, 1868, the son of a jeweller of the same name. He was educated at first privately and subsequently at the Leamington Collegiate School. He went up to Caius College, Cambridge, in 1887, receiving his clinical training at St. George's Hospital. He graduated M.B., B.Chir. in 1904 and proceeded M.D. in 1906. Elected M.R.C.P. in 1898, he became a Fellow of the College in 1907. After graduation he held a number of appointments at St. George's and had good hopes that he would get on its staff. Unfortunately for him, when the time came to seek an honorary appointment there seemed to be no prospect of a vacancy in the foreseeable future. Accordingly, when a vacancy arose at Charing Cross Hospital he applied for it and was elected to the staff as an assistant physician. Six months later a death vacancy occurred at St. George's Hospital, but Fenton felt that he could not honourably apply for the post, having been elected so recently to the staff at Charing Cross, though his election would have been nearly a foregone conclusion. This decision was much to his credit, as the St. George's Hospital students at that time usually went into a type of practice which produced a much higher proportion of lucrative private consulting practice than did those from Charing Cross. Shortly after his election to the staff at Charing Cross he became assistant physician at Brompton Hospital, and when the National Insurance Act of 1911 was implemented he became medical officer in charge of the Chelsea tuberculosis dispensary, which was located at Brompton.

When Fenton became dean of the Charing Cross Hospital Medical School he found it in rather a precarious condition, and he worked very hard to rehabilitate it. Unfortunately he had a long period of ill-health, and because of various things that went wrong subsequently, but through no fault of his own, he nevertheless felt compelled to resign. He was also dean of the medical school at Brompton Hospital. He retired from the staff of Charing Cross in 1933, but owing to the rules at that time in force at Brompton he remained on the staff at that hospital till 1939. On his retirement he was appointed consulting physician to both hospitals. He was an examiner in medicine for the Royal College of Physicians, Cambridge University, and the University of Wales, and also for the Society of Apothecaries of London. His contributions to the literature of medicine were not many, but he was joint author with the late L. S. T. Burrell of a textbook entitled *The Diseases of the Chest*. At the time of his death he was one of the most senior Fellows of the Royal College of Physicians.

F. H. Y. writes: With the passing of W. J. Fenton we have lost one of the specialists in diseases of the chest who

practised in the pre-*x*-ray era of chest medicine. But when in the early 1920's the value of *x* rays became clear Fenton was quick to realize this, and during the controversy about the respective merits of *x* rays and clinical signs in the early diagnosis of tuberculosis he was not one of the die-hards. Fenton was a very capable and painstaking consultant in chest diseases, though he had no special bent for original work. Most punctilious in his duties at his hospital, he was very popular with his hospital patients because of his kindly disposition. Some of his best work was done at the Chelsea tuberculosis dispensary, where his interest in the preventive side of tuberculosis work was given full scope. Apart from his professional work, his absorbing interest was photography, and he was an enthusiastic worker in bromoils. His holidays were spent in taking landscape and architectural photographs. After his retirement in 1939 he took many photographs, mainly in Worcestershire and Warwickshire, for the national records. He was also a keen violinist and at one time conducted an amateur orchestra. A shy man, he did not make friends easily, but those who did penetrate below the surface were impressed by his sterling worth. He married, rather late in life, Vivian Olive Ferguson. The marriage was happy, and her early death, after 16 years of marriage, in 1930 was a sad blow and left a permanent mark on him. He had one daughter and two sons, one of whom was killed on active service during the second world war.

EDITH M. HALL, M.D., F.R.C.S., F.R.C.O.G.

Miss Edith M. Hall, gynaecological and obstetric surgeon to the South London Hospital for Women, died in London on December 26, 1957, aged 61.

Edith May Hall was born at Westbury, Wiltshire, on May 9, 1896. From childhood she was determined to become a doctor, and she entered the London (Royal Free Hospital) School of Medicine for Women in 1914. After a distinguished undergraduate career she graduated M.B., B.S., with honours in surgery, in 1920. Two years later she proceeded M.D., winning the university medal in midwifery and gynaecology. In 1931 she took the F.R.C.S. and was elected F.R.C.O.G. in 1940. After qualification she held junior house appointments at the Royal Free Hospital and the posts of junior and senior resident medical officer at Queen Charlotte's Hospital. She then returned to the Royal Free to join the obstetric and gynaecological unit there, eventually becoming senior assistant. At the Annual Meeting of the B.M.A. in 1923 she was secretary of the Section of Obstetrics and Gynaecology.

Miss Hall's first consultant appointment was to the Mothers' Hospital, Clapton, in 1923, and she remained consultant obstetrician to this hospital until 1949. One of the original members of the staff of the Marie Curie Hospital, she held her appointment there until the time of her death. At the London Homoeopathic Hospital, in 1926, she was the first woman to be elected to the staff. In 1935 she joined the staff of the South London Hospital for Women and Children as a gynaecologist, and later, when the midwifery department was opened, she was appointed consultant obstetrician to the hospital. During the war years she undertook general surgical duties there in the Emergency Medical Service and was responsible with her colleagues for the treatment of air-raid casualties. Owing to failing health she resigned her appointments at the South London Hospital in 1956.

D. McN. writes: Edith Hall was at all times of her life an inspiration to her friends, patients, and colleagues. Her kindly and affectionate nature made it possible for her to appreciate the troubles and difficulties of others, and the efficiency of her work made her opinion always highly valued. We at the South London Hospital have lost in her passing one of our most distinguished colleagues and one who has done much for the present status of the hospital. She will be remembered essentially as a teacher of generations of students, house-officers, and professional colleagues. Her personality was such that by her example and courage she did good to all with whom she came into contact. This is the Edith Hall whom we knew and loved.

Edith Hall died at her home in Hampstead after a long illness spent in part at the South London Hospital. Her colleagues would like, whilst paying tribute to Edith's memory, also to pay tribute to the devoted care given her during her long and difficult illness by Dr. Olive Rendel and by her sister, Dr. Marjorie Hall, to whom our sympathy goes out.

A general-practitioner friend writes: A ripple of spontaneous and joyous laughter; an integrity which nothing could shake; a kindly presence and courteous manner, linked with an insight and interest in each as a person, and not as a surgical case, which produced the utter trust and confidence of every patient, however nervous; a conscientiousness and skill in her work which called forth the utmost trust of her colleagues; an unswerving answer to the call of duty, and yet a delightful abandonment in private life; a marvellous and unselfish patience in her last illness—this portrays Edith Hall.

H. G. BEDFORD RUSSELL, B.Chir., F.R.C.S.

Mr. H. G. Bedford Russell, consulting surgeon to the throat department of St. Bartholomew's Hospital, died at his home in Sandford St. Martin, Oxfordshire, on December 30, 1957, aged 71. He was widely recognized by his colleagues and by his patients as one of the outstanding rhinologists of his day.

Harold George Bedford Russell adopted Britain as his home, for he was born in Australia in 1886, the second son of F. R. Russell. He received his early education at Geelong College and came to Sidney Sussex College, Cambridge, to study medicine; he continued his clinical studies at St. Bartholomew's Hospital, qualifying with the Conjoint diplomas in 1911, and graduating B.Ch. in the following year. At Bart's he held the resident posts of house-surgeon and ear, nose, and throat house-surgeon. During the first world war he served with great distinction in the British Expeditionary Force in France, becoming D.A.D.M.S. to the 9th Corps, being mentioned in dispatches and awarded the Croix de Guerre. Upon his return to England he was stationed at the Queen's Hospital, Sidcup, which had been set up as a centre for the treatment of facial injuries in the days when facio-maxillary surgery was in its infancy. Continuing the study of his chosen specialty, he took the F.R.C.S. in 1919, and later he was appointed to the staff of the Throat Hospital, Golden Square, and surgeon to the throat department of his old hospital, St. Bartholomew's. Subsequently he became surgeon in charge of this department. His keen interest in research led to his appointment as director of the investigation wing at the Metropolitan Ear, Nose, and Throat Hospital, London, during the second world war. When the B.M.A. held its Annual Meeting in Winnipeg in 1931 he was vice-president of the Section of Oto-Rhino-Laryngology. After his retirement from active hospital work he continued to practise privately and to carry on with his research.

F. B. K. writes: Mr. Bedford Russell devoted much of his professional life to the study of nasal disease and was one of the first to follow Arthur Proetz by treating sinusitis by displacement therapy. In his busy years of investigating, practising, and teaching he found time to contribute many articles on varying aspects of paranasal sinus disease. His approach to this problem was both theoretical and practical. In addition to having a vast knowledge of the subject, he was an extremely able and efficient operator. His outstanding contribution was his insistence on the importance of the relationship between dental sepsis and maxillary sinusitis, and on the association between mental disorders and sinusitis. He was an ardent advocate of

radical surgical extirpation of the ethmoidal and sphenoidal sinuses when inflammatory changes were irreversible, his convictions in this aspect of therapy owing much to the influence of Fenis Smith, whose work he held in high regard.

His interests outside medicine were wide and varied and included a love of athletics and of gardening; he was especially keen on tennis and the cultivation of roses. His charming smile, friendly approach, sunny personality, kindness, and understanding endeared his patients to him, and his keen sense of humour, quick intelligence, loyalty, and helpfulness were qualities which his colleagues, juniors, and friends will always admire and remember. He bore his long, painful, mortal illness with the greatest courage, and despite his great suffering he carried on to the last, the old smile breaking through and irradiating all who visited his Harley Street consulting-room where he remained until nine days before his death.

He is survived by his wife, Lilian, whom he married in 1928, and by his two sons. He will be sorely missed by his colleagues and by his many patients and friends.

T. H. C. BENIANS, F.R.C.S.

Dr. T. H. C. Benians, honorary consulting pathologist to the Prince of Wales's General Hospital and to the North Middlesex Hospital, died in hospital on January 1, aged 75.

Thomas Herbert Cecil Benians was born at Goudhurst, Kent, on March 13, 1882. He was educated at Goudhurst School and at the London Hospital Medical College, where he won scholarships in anatomy and physiology. He qualified in 1907, and, being interested in pathology even at that early stage in his career, he became an assistant in the pathological department and later in the inoculation department at the London Hospital. He was also for a time prosector at the Royal College of Surgeons, of which he became a Fellow in 1913. In 1914 he was appointed pathologist to the Prince of Wales's General Hospital, and he remained in that post until his retirement in 1951. During the first world war he undertook part-time work as pathologist and director of laboratories at Addington Park War Hospital. In later years he was also pathologist to the North Middlesex and Enfield Hospitals. At the end of the second world war he took up a whole-time appointment at the Prince of Wales's General Hospital, and when the National Health Service came into being he became pathologist to the Tottenham Hospital Group. After his retirement he occasionally worked as a locumtenent at other hospitals, and he was occupied until shortly before his death with his research work, which he was able to continue at his old laboratory at the Prince of Wales's General Hospital.

Bacteriology and immunity were his chief interests, and he wrote many papers in this and other journals on such subjects as the staining properties of bacteria, the bacteriology of cerebrospinal fever, septicaemia, and cold agglutinins. But he was a good all-round pathologist as well, and during the second world war he did much to build up the blood transfusion service at the North Middlesex Hospital. For many years he was dean and lecturer in pathology and bacteriology at the old North-East London Postgraduate Medical College. After he had succeeded in including the North Middlesex and, later, the Chase Farm Hospitals in the work of the college, the North London Postgraduate Medical Institute came into being. The pathological museums of the institute are formed around the nucleus collected by Benians and his staff.

Shortly after he qualified Benians worked for a time in Rhodesia and South Africa, where he met his wife, formerly Miss Aimée Rogers. She survives him, together with two sons and a daughter.

B. H. J. writes: Tommy Benians was a popular figure at the Prince of Wales's General Hospital, and generations of housemen came to regard him as a father confessor who would give sound advice on pathology and on many other matters not necessarily related to professional work. At lunch time he would often recount little incidents with great enjoyment, but never with malice and never in a manner to cause any hurt. Benians never claimed to be a clinician, but his advice on further investigations that might prove fruitful was often sought and often resulted in the solution of a clinical problem. Gardening and the growing of flowers gave great pleasure to Benians, and when he lived in a flat during his latter years he maintained a small allotment, which was a continual source of joy to his wife and himself.

At the Prince of Wales's General Hospital we have lost a dear friend, and our sympathy is extended to his widow and children.

Sir PHILIP MANSON-BAHR writes: Benians always remained a loyal son of the London Hospital, and my recollections of him go back well over fifty years, since we were students together in those halcyon days. He always remained the same. His manner and approach never deviated from early times. We met often before the wars and between the wars and yet his countenance and manner were just as serene and unruffled as of yore. It was always a refreshing experience because of his whimsical humour and sardonic smiles. In many ways Benians possessed originality: he had something new and unexpected to add to every problem, especially when some tropical parasite impinged upon some theory of his own. In recent years we were drawn together by the magic of the pen and brush. He was a keen member of the Medical Art Society, and his compositions, which so adequately expressed his personality, graced our annual exhibitions. It must be appreciated, too, that his contributions to bacteriology and pathology were not inconsiderable.

PEYTON BEALE, F.R.C.S.

Mr. Peyton Beale, honorary consulting surgeon to King's College Hospital, and senior Fellow of the Royal College of Surgeons of England, died peacefully on Christmas Eve, 1957, aged 93.

Peyton Todd Bowman Beale was born in London on June 20, 1864, the son of Professor Lionel S. Beale, F.R.S., professor of medicine at King's College, London, and the grandson of Dr. Lionel John Beale. From Westminster School he won a junior scholarship to King's College and qualified L.S.A. in 1888, took the London Conjoint diploma in the following year, and was admitted F.R.C.S. in 1890. After qualification he held the appointment of house-surgeon at King's College Hospital, and was elected to the staff as assistant surgeon in 1893. He became full surgeon in 1901 and retired in 1910, being elected a consulting surgeon in 1925. At King's College Peyton Beale was lecturer in biology from 1891 to 1900 and demonstrator in physiology and histology from 1891 to 1904; for some years he was also lecturer in physiology and artistic anatomy in King's College for Women. He wrote a book on elementary biology (1894) and also *Aids to Physiology* (1903). He was elected a Fellow of King's College in 1909. From 1906 to 1910 he was dean of the faculty of medicine of King's College. This was at the time when the medical school of King's College Hospital was separated from the medical department of King's College, and consequently Peyton Beale had to carry much of the administrative burden when the change was made, and he was in fact the first dean when the present medical school came into existence in 1909. A member of the surgical staff of the Great Northern Central (now the Royal Northern) Hospital over a long period, he was elected consulting surgeon when he retired from practice in London. He was an examiner in physiology, and later in surgery, to the Society of Apothecaries of London, and also examined in surgery for Glasgow University and in biology for the London Conjoint Board.

Peyton Beale left London in 1910 to practise in Southampton. About ten years later he moved to a house near Milford-on-Sea, where he was on the staff of the local cottage hospital as consulting surgeon. He had many hobbies, being a keen botanist and microscopist, and an expert

carpenter and metal-worker. He and his wife, formerly Miss Gertrude Attwell, celebrated their golden wedding in 1942. Mrs. Beale died in 1949. They had two daughters.

J. P. J. JENKINS, O.B.E., M.R.C.S.

Dr. J. P. J. Jenkins, of Griffithstown, Monmouthshire, died suddenly at Cardiff on December 12, aged 68.

Doctor, soldier, sportsman, and an outstanding personality, John Powell Jones Jenkins was born on August 16, 1889, the son of the late John Jenkins, of Llantwit Vadre, Glamorganshire. Educated at Christ's Hospital, Cardiff High School, and the Westminster Hospital, he qualified in 1918, took up general practice at Pontypool in 1921, and a year later married Miss Muriel Everett, the daughter of a prominent Pontypool solicitor. In the first world war he served in the R.A.M.C. in France, Mesopotamia, and Salonika. Mobilized before the outbreak of the second world war, he commanded field ambulances both in France and in the ill-fated Norwegian campaign. He later went to West Africa to set up and maintain a large hospital there, but returned to take charge from 1944 to 1945 of a large general hospital of 2,000 beds in Louvain. While he was there he was made an Honorary Member of the University of Louvain, decorated with the Order of Leopold, and mentioned in dispatches. In 1945 he was appointed O.B.E. for distinguished war services, and he became a Deputy Lieutenant for the County of Monmouthshire in 1947. For 35 years of outstanding service to the St. John Ambulance Brigade he was, in 1956, invested as a Knight of the Order.

T. B. writes: Colonel Jenkins was a keen sportsman and was very proud of his appointment as medical officer to the British team at the Olympic Games in Helsinki. "P. J.," as he was affectionately known, was a prominent figure in medical circles in Wales. A past chairman of the Monmouthshire Division and a past president of the South Wales and Monmouthshire Branch of the B.M.A., he was, up to the time of his death, treasurer of both. A leading member of the Welsh Faculty of the College of General Practitioners, he was the treasurer since its inception. As nominee of the senior medical and dental staff, he served for many years on the Newport and East Monmouthshire hospital management committee, until he was appointed as the first general-practitioner nominee in Wales to the Welsh Regional Hospital Board, being an active member of many of the latter's most important committees until his death. He was the first chairman of the local medical committee in Monmouthshire and served as a member of the Monmouthshire and Newport executive council, relinquishing these appointments at his own request. At his memorial service on December 14 representatives of medicine, the ambulance service, sport, and the general public overflowed from the church—a worthy tribute to a wonderful person. Adequate words cannot be found to describe "P. J.": he was a born mixer, a forthright debater, and a great-hearted doctor. We who have been fortunate enough to have known him intimately will feel that there remains with us always a gap that none can fill. Our sympathy goes out to his wife, who is a chairman of the juvenile court of the Pontypool magistrates, his son, Dr. Richard Jenkins, a senior registrar at the Westminster Hospital, and his two daughters.

J. L. PAWAN, M.B.E., M.B., Ch.B., D.P.H.

Dr. J. L. Pawan, formerly bacteriologist and pathologist to the government of Trinidad and Tobago, British West Indies, died at his home at Port of Spain, Trinidad, on November 3, 1957. He was 70 years of age.

Joseph Lennox Pawan was born in Trinidad on September 6, 1887. From St. Mary College, Trinidad, he entered Edinburgh University as a medical student, and graduated M.B., Ch.B. in 1912. Returning to Trinidad after graduation, he was assistant surgeon at the Colonial Hospital there from 1913 to 1916, district medical officer to Tobago for the next three years, and to Cedros, Trinidad, from 1919 to 1922. He then revisited the United Kingdom to take the D.P.H. of the English Royal Colleges in 1923, and followed this success with postgraduate work at the Pasteur Institute in Paris and in Germany. Later in 1923 he was appointed bacteriologist to the Government of Trinidad, becoming also pathologist and pathological registrar to the Colonial Hospital. He held these appointments for twenty-five years. He published various papers on serum calcium levels, pulmonary tuberculosis, sleeping sickness, and the bacteriology of water supplies and food-poisoning in the tropics, but his outstanding work was on the transmission of paralytic rabies by the vampire bat, and the pathology and histology of the experimental disease, work for which he was appointed M.B.E. in 1934. He visited America in 1954 as special consultant on rabies to the United States Government, and in the same year was invited to become co-chairman of the rabies committee of the World Health Organization, but ill-health forced him to decline this invitation. He is survived by his wife, one son, and two daughters.

H. G. F. DAWSON, L.R.C.P.&S.I.

Dr. H. G. F. Dawson, who was in general practice at Birkenhead for over fifty years, died on November 3 at the age of 85.

Harry George Frederick Dawson was born at Kildare in February, 1872, and was educated at Denstone College and Trinity College, Dublin, qualifying by taking the Irish Conjoint diploma in 1895. He then held several appointments at the City of Dublin Hospital, and for a time was clinical clerk at the Coombe Lying-in Hospital. In 1898 he settled in general practice at Birkenhead, and was actively engaged in this work until his retirement in 1949. During the first world war he served in Gallipoli, Palestine, the Sudan, and Cyprus. He had had a long association with the Territorial Army, and in 1920 was awarded the Territorial Decoration. A member of the British Medical Association for fifty-nine years, he was at one time chairman of the Birkenhead Division. Keenly interested in public affairs, he was elected a member of the Birkenhead borough council in 1910, and later became chairman of a number of its committees, including the public health committee. He resigned from the council when he retired from practice. He is survived by two married daughters.

CLIFFORD WHITE, M.D., F.R.C.P., F.R.C.S. F.R.C.O.G.

Professor F. J. BROWNE writes from Sydney, Australia:

I was grieved and more than mildly shocked to read in the *Journal* of November 2, just arrived here, of Clifford White's death. Somehow one never thought of the possibility of Clifford dying. Like "Jock" Hedley, age did not seem to wither him. He looked perpetually young, and through the years that I knew him at U.C.H. he never seemed to change—no grey hairs, always elegant and well groomed, and gifted with an acid but not too mordant wit that often delighted his colleagues, nurses, and students. He was a master of operative technique—in the class of Charles Read and Louis Carnac Rivett—and his abdominal work was a joy to watch, though it could be depressing to onlookers less dexterous than himself.

It is surprising that in the otherwise excellent biographies published in the *Journal* there is no mention of his classical contribution to obstetric literature through his paper entitled "The Contraction Ring as a Cause of Dystocia." This was read before the Royal Society of Medicine on December 6, 1912, and was published in abstract form in the *Lancet* in 1913. In it, from his experience of three cases and examination of three specimens, he distinguished clearly and for the first time between contraction ring and retraction ring, and gave twelve points of difference between them. He also discussed the causes of contraction ring (or constriction ring, as it is now called) and its clinical features, diagnosis, and treatment so thoroughly that no significant addition to our knowledge has been made since, almost certainly because none has seemed necessary.

Medico-Legal

"AUTOMATISM" AS A DEFENCE

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

When Kenneth Baxter, of St. Leonards Gardens, Hove, was prosecuted before the Brighton justices on a charge of driving a motor-van dangerously, the facts found by the justices were that on April 12, 1957, when on his way to Withdean, he remembered being in Preston Circus but thereafter remembered nothing until he found himself searching for his glasses after the accident which had occurred. In fact his van failed to stop at a halt sign in Springfield Road, Brighton, passed straight across a road junction, collided with a car, carried on for a short distance, and then overturned. For the defence it was submitted that the loss of memory could only be attributed to Mr. Baxter being overcome by some illness without warning, and the justices accepted the proposition that, although he must have exercised skill in driving in order to reach Springfield Road, he was not conscious of what he was doing after leaving Preston Circus and was not capable of forming any intention as to his manner of driving. He was accordingly acquitted.

The prosecution appealed, and on December 19 the Divisional Court of the Queen's Bench Division delivered their reserved judgment allowing the appeal.[1] In his judgment the Lord Chief Justice said that section 11 of the Road Traffic Act, 1930, contained an absolute prohibition against driving dangerously. No question of intention entered into the offence, and the justices' finding that Mr. Baxter was not capable of forming any intention as to his driving was really immaterial. What they meant was that he was in a state of automatism, but the onus of proving he was in that state was on him. It was akin to the defence of insanity, and the rule of evidence was that it was for a party who asserted something which lay exclusively within his knowledge to prove it. All that Mr. Baxter's evidence did prove—and the justices were entitled to believe it—was that after the accident he could not remember what happened after he left Preston Circus. This was consistent with his having fallen asleep, which was not an uncommon cause of serious accidents, and it would be disastrous to hold that falling asleep at the wheel was a defence. There might be cases in which the accused could be said not to be driving at all, but in this case the evidence fell far short of what would justify a Court in holding Mr. Baxter was in a state of automatism. There was no reported case in England or Scotland where a defence of automatism had been set up or been the subject of judicial decision.

Mr. Justice Devlin, agreeing that the evidence was insufficient to justify the magistrates' decision, considered the question of automatism in relation to criminal responsibility. It was novel, and the answer would depend, among other things, on whether intention was a necessary ingredient of the offence charged. Since Mr. Baxter had not challenged the normal legal presumption that he was sane, the justices could not presume that he was suffering from a disease of the mind. Unless the evidence showed that his irrationality was due to some other cause, the justices were not entitled to acquit. The criminal law recognized two categories of mental irresponsibility: where the disorder was due to disease, and where it was not. If disease was not the cause, if there was some temporary loss of consciousness arising accidentally, it was reasonable to hope that it would not be repeated and that it was safe to let the acquitted man go free. If disease was the cause, the same thing might happen again, and so, although the accused was not criminally responsible, the special verdict of insanity followed by indefinite detention in what used to be called a criminal lunatic asylum was the law's solution. Whatever the legal theory might be, mental disease was in practice therefore not available as an excuse for the commission of any of the lesser crimes.

[1] *The Times*, December 20, 1957.

Mr. Justice Pearson agreed. He said that in cases where a man had an epileptic fit, or was unconscious by reason of the onset of disease, or was stunned by a blow on the head from a stone, or was attacked by a swarm of bees so that for the time being he was disabled and any movements of his arms and legs were caused by the action of the bees, it could be said that at the material time he was not driving and therefore was not driving dangerously. In the present case there was a finding of the justices that he was driving, and no evidence to support the justices' decision that he was not driving dangerously.

The Divisional Court therefore allowed the appeal on the ground that there was no evidence to support the defence of automatism which had been put forward. But the Court recognized that in principle if someone acts in a state of automatism induced by some cause other than insanity, and can prove it by acceptable evidence, he is not criminally responsible for acts committed while in that state, just as the insane man within the McNaughton Rules is not criminally responsible for acts committed while he is insane. As the Lord Chief Justice observed, there are no reported cases yet. It remains to be seen whether anyone will be able to establish by evidence what will be necessary to bring him within the principles canvassed in this case, and to what extent the House of Lords would endorse those principles if an appeal in such a case ever reached it.

Vital Statistics

RESPIRATORY DISEASES

REPORTS FROM GENERAL PRACTITIONERS

Dr. G. I. WATSON (Peaslake, Surrey) writes: During December, 1957, influenza continued to be the commonest disease affecting patients in this country practice, and the Asian strain of virus A was isolated for the fourth time since September. One small school, not previously much affected, had a sharp epidemic involving all the remaining 11 non-immune pupils and staff. In the villages the disease has mainly affected adults with contacts outside the practice area—for example, Guildford, London, and Bournemouth. Three patients apparently had a second attack, two of them schoolboys; both attacks were short-lived but associated with other cases in the same house on each occasion. Otherwise, those at present being affected did not have the disease earlier and have had little or no contact with schoolchildren, who formed the bulk of the cases in the autumn.

There were 8 cases of pneumonia or bronchopneumonia (no deaths) among the 41 typical or probable cases of influenza during the month. One further case of undue bradycardia occurred in a male, aged 30 (temperature 101.4° F. (38.6° C.), pulse 68 lying, but 40 when he sat up). The incidence of acute bronchitis with asthma, however, and of other acute or subacute respiratory diseases did not significantly differ in December, 1957, from 1956 (Table I).

TABLE I.—*New Visits in December, 1957, Compared with 1956*

Disease	1957	1956
Influenza, typical	20	0
Influenza, probable	13	3
P.U.O. without respiratory symptoms	0	5
Pneumonia and bronchopneumonia	8	2
Total	41	10
Acute bronchitis and asthma	6	5
Acute tonsillitis	7	9
Acute otitis media	4	2
Coughs, colds, sinusitis or "catarrh"	4	2
Diarrhoea and or vomiting	11	5
Acute abdominal pain and nausea	4	3
Other new visits	40	43
Total	85	79
Total new visits	126	89

There was a noticeable difference between the age and sex of patients with influenzal pneumonia and those with acute bronchitis and asthma. Influenzal pneumonia was commoner in women, not only in December but throughout the

epidemic; while acute bronchitis with asthma ocurred more commonly in males (Table II).

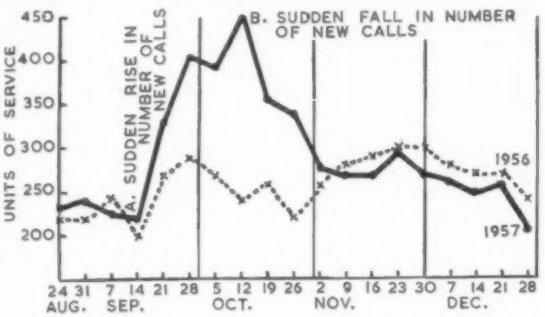
TABLE II.—*Age and Sex of Patients with Pneumonia and Acute Bronchitis, December, 1957*

Pneumonia (Probably Influenzal)			Acute Bronchitis with Asthma		
Age	M	F	Age	M	F
20–49	—	2	0–10	3	—
50–69	1	3	11–69	1	—
70–89	—	2	70–89	1	1
Total ..	1	7	Total ..	5	1

Virus studies carried out in this practice during the influenza epidemic (unpublished) suggest that there has been a high rate of subclinical infection among those in house contact with influenza, but that casual contact of short duration was often insufficient to provoke an immune reaction. This means that many parents whose schoolchildren were affected during the autumn epidemic will have acquired resistance against further infection, but that adult communities and assemblies not previously affected may become centres from which sporadic cases are spread to their dormitory towns and villages.

More Chest Disease

Drs. W. J. MELDRUM, C. A. H. WATTS, and H. F. CANTWELL (Ibstock, Leics) write: The Asian type of influenza started and stopped quite abruptly in this area. Once new cases of the disease had ceased to occur in epidemic proportions the number of new cases fell sharply to the seasonal normal. There were still a few sporadic cases in the weeks that followed the main outbreak, but these became more scanty, and from the end of October there were virtually none. Indeed, the work of the practice fell below normal. This is shown in the Chart, where the trend of the practice figures is shown for the years 1956 and 1957.

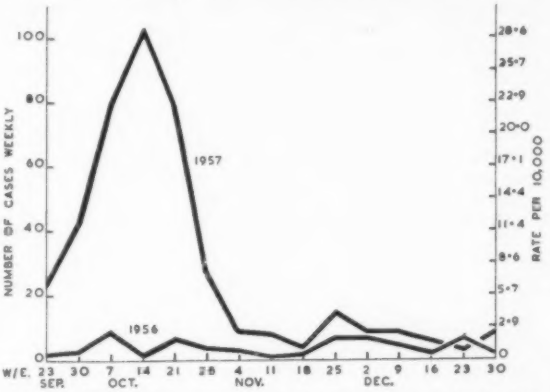


Early in December cases of influenza began to reappear in small numbers. Sometimes a whole family unit was laid low by the disease, and it is significant that these were almost always individuals or family units who had escaped the major epidemic. There was no noticeable rise in the incidence of pneumonia. This may in part be due to the prompt exhibition of antibiotics to known chest risks. While there was no appreciable increase in febrile catarrhal states, there was a distinct rise in the figures for chest diseases, as if some factor had upset the asthmatic, the bronchiectatic, and the chronic bronchitic type of patient. An analysis of cases seen at the surgery in December for the years 1956 and 1957 reads as follows:

Year	Upper Respiratory Infections, %	Chest Disease %	Total % of Surgery Work
1956	8·3	3·8	12·1
1957	7·0	9·3	16·3

Prevalent Abdominal Disorder

Dr. R. E. HOPE SIMPSON (Cirencester, Glos) writes: Despite press statements, we have little to report in Cirencester on the incidence of respiratory diseases. After the epidemic in September and October clinical influenza fell rapidly, and, as will be seen from the accompanying Chart, it has remained at a low level ever since. 1956 was a notably mild year for influenza, and the Chart shows that in December, 1957, influenza reached a similar low level.



Clinical influenza in a general practice in Cirencester in the last quarter of 1956 and 1957. Weekly totals of cases and incidence.

In Cirencester at the moment there is no augury of an unusual incidence later in the season. Colds also are probably a little less frequent than usual for the time of year and show no peculiar features. The cases of influenza which do occur differ from the Asian type epidemic chiefly in the age of person attacked and the less violent onset. We have not so far been able to isolate the causal organism. There is in this area a widespread outbreak of abdominal disorder characterized by severe vomiting, sometimes accompanied by abdominal pain and diarrhoea and a slightly raised temperature. This visitation began well before Christmas and has a high incidence.

TABLE I.—*Distribution, According to School Status, of Cases of Clinical Influenza in Last Quarter of 1956, During the Asian Type Epidemic, 1957, and During the Subsequent Weeks of 1957*

Age Group	Sept. 17, '56–Dec. 31, '56	Sept. 17, '57–Nov. 4, '57	Nov. 5, '57–Dec. 31, '57
Below school age ..	21·2%	9·7%	15·8%
School age	16·7%	31·0%	10·5%
Above school age ..	62·1%	59·3%	73·7%

Tonsillitis and Pharyngitis

Dr. F. H. STAINES (Callington, Cornwall) writes: The influenza, previously reported, ceased to be epidemic in this practice about November 6, 1957, but has not yet ceased entirely. During the rest of November and the first half of December an average of one new case daily was seen; the rate has now dropped to 3 cases per week.

The general level of respiratory infections is now unusually high; the total rate is about two-thirds that of the peak rate of the influenza epidemic in October. The normal pre-Christmas "slack" did not occur this year, and the post-Christmas "rush" was therefore less obvious, though abnormally great.

In mid-December there was a short, sharp epidemic, mainly among children, of a tonsillitis which was not accompanied by nasal catarrh, glandular enlargement, or otitis—about 15–18 cases (our practice is of about 3,400 patients). One child and one adult were severely ill for more than a week. No similar case has been seen in the last ten days.

Just before Christmas a different complaint started, again mainly among children under 10. The symptoms were sore throat, cough, and in one-third to one-half the cases earache. The signs were, in all cases, a mild pharyngitis, a

few neck glands, and a short-lived moderate pyrexia—100°–101° F. (37.8–38.3° C.). Some of these patients had a red tongue, two had running eyes, some had scattered moist sounds in the chest, and all those complaining of ear pain (and some who did not) were seen to have a myringitis rather than a true otitis media, on one or both sides. 13 new patients with this clinical picture have been seen in the last seven days. All cases so far have been short and benign.

Both classical pneumonia and true bronchitis are uncommon here—the chronic bronchitics of the practice can be counted on two hands—and sinusitis as a complication of the ever-present upper-respiratory catarrhal conditions is regularly, though not frequently, seen.

During December, though purulent nasal catarrh has been a relatively infrequent cause of consultation, sinusitis has been unusually prevalent. There has been more acute bronchitis in the last two weeks than we have seen in any similar period in the last five years. Twelve new cases have been seen in the past week, with an age-range from infancy to the 80's. Five cases of classical pneumonia have been seen:

(1) Girl aged 13. Prolonged course, multilobar, of moderate severity and low toxicity. Culture gave mixed growth of *Str. viridans* and *B. coli* resistant to penicillin and erythromycin, sensitive to chloramphenicol and tetracylines.

(2) Male aged 80. Single lobar pneumonia, concurrent with another illness (jaundice, probably infective, possibly neoplastic); rapid response to penicillin.

(3) Girl aged 2. Found ("We weren't going to call you, doctor, but as you're next door, would you mind?") to be recovering from right upper-lobe infection. No response to penicillin, rapid clinical recovery with tetracycline.

(4) Boy aged 3. Probable single lower-lobe infection. Rapid response to penicillin.

(5) Female aged 73, hypertensive. Satisfactory recovery from single basal lobar infection on tetracycline.

Of 6 deaths in the practice during December, 1957, one was due to an acute bronchitis finally and suddenly overloading a failing myocardium; and 2 (both patients aged over 80) seemed to be due to simple senility 4 to 6 weeks after apparently satisfactory recovery from the epidemic influenza.

Finally, in retrospect, during the main influenza peak two other possible virus infections were seen in unusual numbers. Five cases (all adults) resembling epidemic vertigo, and about 8 resembling the winter vomiting disease, were seen. All may have been influenzal variants, but the former, at least, did not appear to be such.

Distinct Respiratory Infection

Drs. JOHN FRY and G. E. H. CALLEBAUT (Beckenham, Kent) write: The last quarter of 1957 produced a very high rate of acute respiratory infections in this area. From September till the end of October the influenza-A epidemic was at its height. There was a sudden and short-lived lull in the first two weeks of November, and then from the week of November 18 a fresh epidemic of acute respiratory illness has been prevailing. This latter epidemic appears to be clinically distinct from the influenza epidemic of September and October and from the usual seasonal coughs and colds.

Although not nearly so widespread as the influenza, when almost 1,000 patients were seen, it is estimated that so far around 250 of our patients have suffered, in the past four weeks, from this distinctive acute respiratory infection, and there is as yet no sign of any decline. The clinical features are a gradual onset of malaise and shivering, followed by a raw throat and chest and a cough which soon becomes productive of mucoid sputum. There is a variable degree of systemic disturbance, with a fever of around 100–101° F. (37.8–38.3° C.). Backache, aching limbs, and sore eyes were not common features. The acute illness persisted for four to five days. It is of interest and some importance to note that some 30 of these patients had already suffered from clinical influenza within the preceding three months. All age groups were affected, but there was a predominance of older persons over 40.

During this same period 33 cases of acute bronchitis and pneumonia have been seen, the majority following an acute upper respiratory infection. This is a much higher rate than usual for this time of the year.

Comments.—It appears probable that we have been dealing with a fairly distinct form of acute respiratory infection. It could be differentiated from the seasonal colds by a more severe systemic disturbance, the older age distribution of patients, and the presence of a very troublesome cough, and from influenza by a more gradual onset, less severe systemic disturbance, little aching, and the fact that the 30 patients who had had influenza stated that this illness felt quite different, being less sudden and more drawn out.

No Sign of More Influenza

Drs. PHILIP EDMUNDSON and KEITH HODGKIN (Redcar, Yorks) write: In view of the similarities between the summer pandemic of influenza in 1918 and the recent epidemic, it has been suggested that there may be a second more serious epidemic. An analysis of all diagnoses made in this practice for the past three years has been carried out.

This is a housing estate practice, with a high proportion of children. The figures, which include those for two smaller influenza epidemics, show the monthly incidence per thousand N.H.S. patients for all respiratory and other illnesses, and the Table below shows some of these figures for the year 1957. The comments are based on the three-year analysis.

1957	Influenza Rate 1,000 N.H.S. Pats.	Ac. Bronch. Rate 1,000 N.H.S. Pats.	Pneumonia & Pneumonitis Rate 1,000 N.H.S. Pats.	Coughs Rate 1,000 N.H.S. Pats.	Colds Rate 1,000 N.H.S. Pats.	Ac. Exudat. Tonsillitis Rate 1,000 N.H.S. Pats.	Ac. Enteritis Rate 1,000 N.H.S. Pats.	Boils Rate 1,000 N.H.S. Pats.
Jan. ..	—	22·4	2·1	22·4	5·4	5·0	4·6	5·0
Feb. ..	—	14·1	3·3	15·0	6·7	7·0	5·0	2·5
Mar. ..	—	14·1	2·5	14·1	7·9	8·3	8·3	3·3
April ..	—	11·5	2·4	13·0	2·8	6·2	3·2	6·7
May ..	—	10·3	3·6	11·1	3·2	5·4	5·9	5·1
June ..	—	3·6	1·2	3·6	—	3·9	3·2	2·4
July ..	—	8·5	3·0	4·1	2·6	7·0	6·3	5·2
Aug. ..	0·5	4·8	2·2	2·2	2·2	4·8	3·7	3·7
Sept. ..	133·0	12·2	8·5	7·4	8·1	1·5	5·2	3·3
Oct. ..	54·0	5·2	7·4	6·7	6·3	1·5	4·1	5·6
Nov. ..	2·1	16·3	2·6	19·6	10·0	1·8	6·7	7·8
Dec. ..	0·7	13·7	3·7	17·4	8·9	5·6	12·6	9·6

Influenza.—The present epidemic was 2½ times the size of the 1954 influenza-B epidemic and 10 times that of the 1956 influenza-A epidemic. It was noted that for some weeks after each epidemic we were "conditioned" to making a diagnosis of "influenza" and that cases of acute febrile bronchitis, which showed no epidemic features, were sometimes diagnosed as influenza. This same conditioning may be responsible for the persistently high figures for influenza deaths which are at present recorded by the General Register Office. So far, there is no evidence in this practice of the start of any second epidemic.

Acute Bronchitis.—Criteria of diagnosis: cough, with evidence of fever and moist sounds in chest. The incidence has been little affected by any of the three epidemics.

Pneumonia and Pneumonitis.—Criteria of diagnosis: respiratory illness, with both fever and localizing chest signs, which persists for longer than three days. Apart from the expected increase of cases during each influenza epidemic, the incidence has been very steady.

Acute Exudative Tonsillitis.—Tonsillar redness with exudate showed a striking fall in incidence during the recent epidemic. A similar fall has been recorded in the two previous epidemics (the throats of all patients with influenza were specifically inspected). The monthly incidence (apart from these times) over the three years has been remarkably steady. The significance of this observation is not clear. The figures for the incidence of boils and acute gastro-enteritis were also investigated because we had the impression of big increases following the recent influenza epidemic. Analysis showed, however, that similar increases had not occurred after the previous epidemics and that these present

increases were in fact only small, which shows again the fallacy of relying on clinical impressions alone.

Apyrexial Cases

DR. R. M. MCGREGOR (Hawick, Roxburghshire) writes: In this area during the past four months the family doctor interested in epidemiology has had good opportunity for useful study. The sick rate has remained abnormally high, and National Insurance sickness claims for the week ending September 24, 1957, were 165% over the known seasonal average. During the height of the influenza epidemic, in the week ending October 8, the percentage reached 700. Each successive week thereafter showed a progressive fall until the week ending November 26, when the percentage was still 152 above the average. Since then it has been slowly rising again, and it is now 208% above.

Much of this is caused by the continuing presence of some infective condition. Each week has seen a fresh crop of cases resembling in symptomatology those seen during the peak period of the influenza epidemic, but the complaint of pain in chest, abdomen, and extremities has been much more frequent. The pyrexia has seldom been severe, but has been much more stubborn, particularly in those cases experiencing a second attack, and the degree of anorexia following the attack has been greater. A disconcerting feature has been the number of patients who appear to be quite genuinely suffering discomfort but have been apyrexial throughout, and this type of case has shown a similar lassitude during the recovery stage.

No death has occurred, other than the one already recorded, that could be attributed to influenza. It is known that colleagues have had pneumonic cases, but none has been personally encountered. One case, in an adult male, was very suggestive, since his pyrexia was prolonged for some five days, during which time he had a slight haemoptysis. Subsequent chest radiographs, however, were negative. Incidentally, this was the only case where a drug other than sulphadimidine was administered. He was given penicillin in addition. Sulphadimidine is used as a routine in these pyrexial cases, since it is thought to cause less damage to the stomach mucosa than aspirin and it may play a part in preventing complications. It frequently obviates the need for a constipating cough linctus.

This prolongation of the influenza epidemic has involved mainly the adult population. The old have had a benevolent escape, while the young, proportionately more involved during the explosive phase, have had to contend with other infections. Sporadic outbreaks of chicken-pox, mumps, and measles have been their portion. Fortunately, these infections were all of attenuated virulence.

LATEST NEWS

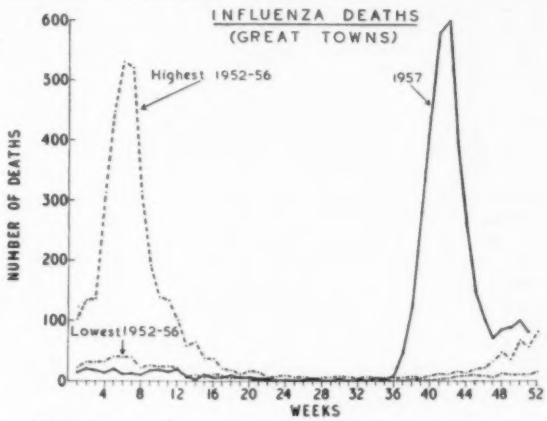
In the great towns of England and Wales in the week ending December 28, 1957, there were 89 deaths from influenza. This number was 7 more than in the previous week and higher than in the corresponding week of any year since 1952, when comparable figures were first published. Deaths from pneumonia numbered 629, being 43 more than in the previous week, while deaths from bronchitis numbered 736, being 87 fewer than in the previous week. Notifications of pneumonia from the whole of England and Wales numbered 755, as compared with 699 the previous week and 400 in the corresponding week of the previous year.

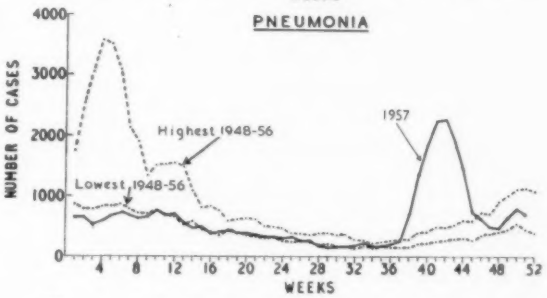
Week Ending December 28

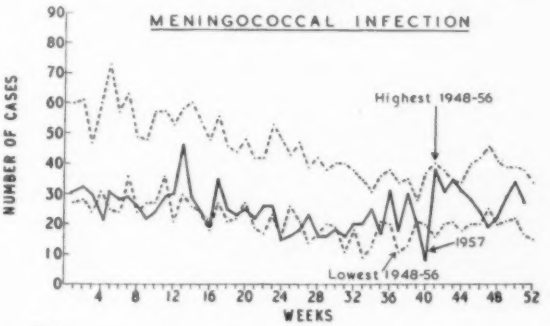
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 576, whooping-cough 257, diphtheria 5, measles 2,022, acute pneumonia 755, acute poliomyelitis 33, dysentery 419, paratyphoid fever 4, typhoid fever 4.

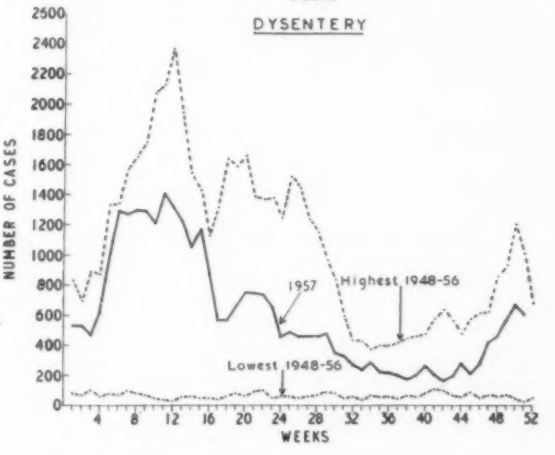
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases (deaths for influenza) of certain diseases notified weekly in England and Wales (great towns for influenza). Highest and lowest figures reported in each week during the years 1948–56 (influenza, 1952–6) are shown thus - - - - -, the figures for 1957 thus ————. Except for the curves showing notifications in 1957, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Scotland in Third Quarter, 1957

The birth rate in Scotland during the September quarter of 1957 was 18.6 per 1,000 population and was 1.1 above the average of the five preceding third quarters. The infant mortality rate was 27 per 1,000 registered live births and was the same as the five-years average. The neonatal mortality rate was 20 per 1,000 live births and was 1 above the rate for the corresponding quarter of 1956. The stillbirths were equivalent to a rate of 23 per 1,000 total births. The death rate was 10.4 per 1,000 population, and was 0.3 above the rate for the preceding September quarter, and 0.4 above the average of the five preceding September quarters.

Deaths from the principal epidemic diseases numbered 104, being 80 more than in the third quarter of 1956. These deaths included 97 from influenza, 5 from meningococcal infections, 1 from whooping-cough, and 1 from measles. The 122 deaths attributed to tuberculosis were 47 fewer than in the third quarter of 1956. 111 of these deaths were ascribed to respiratory tuberculosis. The death rate from all forms of tuberculosis was 9 per 100,000, being 9 below the five-years average. Deaths from malignant disease were 2,706, and were 59 more than in the third quarter of 1956. Deaths from all forms of violence numbered 713, being 98 more than in the preceding September quarter. Of these deaths 153 were due to road accidents, a decrease of 10 compared with the third quarter of 1956.

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in November, 1957, was 117, compared with 107 in the previous month and 118 in November, 1956.

The numbers of cases of industrial diseases in the United Kingdom reported during November, 1957, were as follows: Lead poisoning 7, aniline poisoning 6, chronic benzene poisoning 1, compressed air illness 1, epitheliomatous ulceration 21, chrome ulceration 44; total 80. There were 3 deaths from epitheliomatous ulceration.—*Ministry of Labour Gazette*, December, 1957.

Infectious Diseases

Infectious diseases were less prevalent in England and Wales during the week ending December 21. The decreases in the notifications included 115 for scarlet fever, from 794 to 679, 79 for acute pneumonia, from 778 to 699, 59 for dysentery, from 669 to 610, 53 for whooping-cough, from 504 to 451, and 15 for measles, from 2,450 to 2,435.

The only two notable fluctuations in the trends of measles were an increase of 96 in Glamorganshire, from 293 to 389, and a decrease of 66 in Hertfordshire, from 183 to 117. Only small changes were recorded in the local returns of whooping-cough and scarlet fever. 2 cases of diphtheria were notified, being 1 fewer than in the preceding week. A small decline in the incidence of acute pneumonia was reported from most regions of the country.

6 of the 9 cases of paratyphoid fever were notified in South Westmorland R.D. During the past three weeks 21 cases have been notified in this district.

The notifications of acute poliomyelitis numbered 51, and these were 20 fewer for paralytic and the same number for non-paralytic cases as in the preceding week. The largest return was 6 in Derbyshire (Chesterfield M.B. 2, Staveley U.D. 2).

The largest centres of dysentery were Lancashire 150 (Eccles M.B. 41, Liverpool C.B. 24, Salford C.B. 15, Oldham C.B. 14, Blackburn R.D. 12), London 113 (Islington 26, Hammersmith 21, Stoke Newington 17, Finsbury 16), Yorkshire West Riding 69 (Sheffield C.B. 19, Huddersfield C.B. 16, Leeds C.B. 11), Durham 36 (South Shields C.B. 10, Stanley U.D. 10), Yorkshire North Riding 27 (Easingwold R.D. 26) Staffordshire 21 (Cheadle R.D. 15).

The largest outbreak of food-poisoning was 41 cases in Yorkshire North Riding, Whitby U.D.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 21** (No. 51) and corresponding week 1956.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

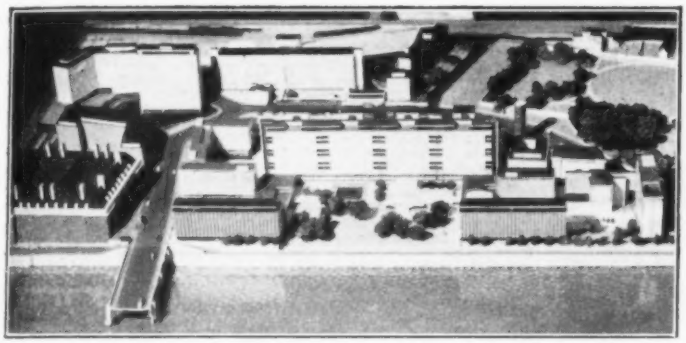
CASES in Countries and London	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire	1956 Eng. & Wales	1956 Lond.	1956 Scot.	1956 N. Ire.	1956 Eire
Diphtheria	2	1	3	0	1	10	2	3	0	2
Dysentery	610	113	163	11	1	696	51	199	4	2
Encephalitis, acute	3	1		0		4	1		0	
Enteric fever:										
Typhoid	2	0	1	0		1	0	0	0	
Paratyphoid	9	0	0	0		2	0	0	0	
Food-poisoning	160	19	9	0		177	25	36	0	
Infective enteritis or diarrhoea under 2 years				8	29				11	25
Measles *	2,435	35	59	43	15	6,575	397	455	180	58
Meningococcal infection	27	1	8	0	2	25	1	8	0	1
Ophthalmia neonatorum	22	0	5	0		18	3	3	0	
Pneumonia †	699	53	416	3	27	465	34	285	7	
Poliomyelitis, acute:										
Paralytic	33	0	0	2	1	42	5	4	1	2
Non-paralytic	18	1				18	2			
Puerperal fever §	166	25	9	1	2	198	31	3	0	
Scarlet fever	679	49	81	9	20	735	53	82	17	13
Tuberculosis:										
Respiratory	467	43	94	26		505	73	118	17	
Non-respiratory	42	3	11	2		70	6	14	7	
Whooping-cough	451	33	23	1	1	1,732	87	366	11	20

DEATHS in Great Towns	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire	1956 Eng. & Wales	1956 Lond.	1956 Scot.	1956 N. Ire.	1956 Eire
Diphtheria	0	0	0	0	0	0	0	0	0	
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		1			
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	1	0	0	2	0	1	0	
Influenza	82	15	3	0	3	14	3	2	1	
Measles		0	0	0	0		0	0	1	
Meningococcal infection		0	0				0	0		
Pneumonia	584	89	38	16	5	285	37	26	14	
Poliomyelitis, acute	3	1		0	0	1	0			
Scarlet fever		0	0	0	0		0	0	0	
Tuberculosis:										
Respiratory	76	8	11	1	3	59	6	11	3	
Non-respiratory		1	0	0	0		2	3	0	
Whooping-cough	1	1	0	0	0	2	0	0	0	
Deaths 0–1 year	233	25	35	11	10	201	19	28	7	
Deaths (excluding stillbirths)	7,719	1176	705	168	187	5,526	755	629	106	
LIVE BIRTHS	7,486	1155	973	176	316	6,607	1059	900	229	
STILLBIRTHS	184	21	24			184	22	15		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

The New St. Thomas's.—St. Thomas's Hospital is to be completely rebuilt on its present site facing the Houses of Parliament. The site will be increased to 8½ acres (3.4 hectares), about twice the present size, with access from the new Lambeth Palace road which is due to be built in 1959–60. The new hospital will provide 827 beds. Excluding the price of land, the total cost of the project is put at about £7m. and is expected to take between nine and twelve years to complete. The rebuilding is planned to be done in four stages so as to interfere as little as possible with the hospital's normal functioning. The governors' plans for the new hospital—which remain subject to certain official consents—were described on January 2 to the press by the chairman of the board of governors, Sir ARTHUR HOWARD, and the hospital's architect, Mr. FOWLER HOWITT. We reproduce above a photograph of a model of the new St. Thomas's looked at from the river side and showing part of Westminster Bridge. Reinforced concrete will be used throughout. The patients' accommodation will be set back about 120 yards (110 m.) from the river and will consist of the main ward block of eleven stories some 140 ft. (42 m.) high, linked to a parallel four-story out-patient block behind it. All the wards will have a clear view over the river. The eight-story residential blocks are placed nearer the river at either end and will be connected to the patients' accommodation by low buildings and colonnades. Provision is also made for the eventual rebuilding of the medical school and for student residential accommodation. The date when building will start cannot be forecast accurately, though at the earliest it will not be before next year. The main hospital block, costing perhaps £4.5m., may well take several years to complete. In the meantime the governors, using their endowment funds, have been buying the land needed and preparing the site. They have already spent more than £250,000 on a block of flats to rehouse displaced tenants.



(Barratt's Photo Press, Ltd.

Institute of Child Health, London University.—Plans for the second stage of the Institute's new building are now ready. It will adjoin the Province of Natal Centre in Guilford Street—the model welfare centre opened in 1955 whose two top floors are the first stage of the new Institute (laboratories, library, and students' common room). The second stage will be a five-story building, comprising the Child Study Centre now in Brunswick Square, the M.R.C. Clinical Genetics Research Unit, the Hospital museum, research laboratories, teaching rooms, a refectory, and administrative offices. The total cost of the new building is put at £220,000. As during the next quinquennium capital funds from London University for medical projects "will be limited because of the preference given to science and technology," the Institute's committee of management has launched a building fund appeal to meet part of the cost. So far, according to the Institute's report for 1956–7, £8,000 has been raised.

Steroid Reference Collection.—Part of the Medical Research Council's Steroid Reference Collection has been transferred to the Postgraduate Medical School of London. In future all requests for compounds in the collection should be addressed to Dr. W. KLYNE, at the Postgraduate Medical School (Ducane Road, London, W.12), and no longer to the National Institute for Medical Research. As a result of generous gifts from two pharmaceutical firms larger supplies of oestriol and 16-epi-oestriol, and very limited supplies of racemic aldosterone, are now available for chemical reference.

Chancellor of Leicester University.—Lord ADRIAN, O.M., F.R.S., is to be installed as Chancellor of Leicester University on June 20.

Royal Society.—The president of the Royal Society has appointed Sir LINDOR BROWN, Sir CHARLES DODDS, and Sir BRYAN MATTHEWS as vice-presidents for the year ending November 30, 1958. The fourth vice-president is Sir WILLIAM PENNEY.

Medical Peers.—The death of Lord WAVERLEY will result in an increase in the number of medical peers, as his heir is Dr. D. A. P. ANDERSON, consultant physician to the Reading group of hospitals. There will now be twelve medical members of the House of Lords. The others are Lord Adrian, Lord Amulree, Lord Boyd-Orr, Lord Cohen, Lord Evans, Lord Haden-Guest, Lord Malvern, Lord Moran, Lord Stamp, Lord Uvedale, and Lord Webb-Johnson.

British Association.—Sir ALEXANDER FLECK, F.R.S., chairman of Imperial Chemical Industries Ltd., was installed on January 3 as this year's president of the British Association for the Advancement of Science. In his inaugural address he announced the British Association's plans for a nation-wide drive to "put across" science to the general public and to the young. The British Association's annual meeting will be held in Glasgow this year, from August 27 to September 3.

Commonwealth Bursaries.—Among those recently awarded bursaries under the Royal Society and Nuffield Foundation Commonwealth scheme were: Dr. A. J. BULLER (St. Thomas's Hospital Medical School, London), to go to Canberra; and Dr. W. P. U. JACKSON (Capetown University), to visit London, Cambridge, and Louvain. Both are to study research techniques.

British Red Cross Society.—Major-General F. C. HILTON-SERGEANT has succeeded Air Commodore H. A. HEWAT as medical adviser to the British Red Cross Society. General Hilton-Sergeant was formerly commandant of the Royal Army Medical College, Millbank.

Adelaide Hospital, Dublin.—An association of Old Students is being formed, but the records available are incomplete. Old Students are asked to notify the secretary of the association, Adelaide Hospital, Peter Street, Dublin.

Professor P. B. Medawar, F.R.S., Jodrell professor of zoology and comparative anatomy at University College, London, was awarded the C.B.E. in the New Year Honours List. The awards to medical men and women are given on p. 87.

Professor W. C. W. Nixon, of University College Hospital, London, is visiting the United States from February 2 to March 5 to lecture at various obstetric centres.

COMING EVENTS

B.B.C. Television.—Visit to the M.R.C. Applied Psychology Research Unit, Cambridge, January 14, 9.45 p.m.

International College of Surgeons.—Scientific trip to U.S.A., March 1–22. Approximate cost 1,300 U.S. dollars (payable in sterling). Details from Dr. J. F. BRAILSFORD, 20, Highfield Road, Edgbaston, Birmingham, 15.

Laboratory Animals Bureau.—Eleventh congress, March 24 and 25, at Birmingham University Medical School. Details from the Bureau, M.R.C. Laboratories, Holly Hill, Hampstead, London, N.W.3.

American Trudeau Society.—53rd annual meeting, May 19–21, in Philadelphia. Further details from the National Tuberculosis Association, 1790, Broadway, New York, 19.

Chemistry Meeting.—A joint meeting of the Society of Chemical Industry and the Italian Chemical Society will be held at Turin, May 25–31. The subjects for discussion include pharmaceuticals, food and agricultural chemistry (pesticides), chemical microbiology, and analytical and physical methods including radio-chemistry. Details from Dr. A. C. C. NEWMAN, The Wellcome Foundation Ltd., 183/193, Euston Road, London, N.W.1.

NEW ISSUES

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 13

GUY'S HOSPITAL.—5 p.m., Endocrine Demonstration: Anorexia Nervosa. Guest speaker, Dr. D. Stafford-Clark.

Tuesday, January 14

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m. Valedictory Address by Dr. W. Mayer-Gross: Psychiatry in an Industrial Community.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. L. E. Glynn: Structure and Stability of Collagen in Relation to Diseases of Connective Tissue.

CHELSEA CLINICAL SOCIETY.—At Rembrandt Hotel, S.W., 8.30 p.m., Mr. A. N. Gilkes: Future of the Independent School.

INSTITUTE OF DERMATOLOGY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. L. E. Glynn: Structure and Stability of Collagen in Relation to Diseases of Connective Tissue.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor F. C. Ormerod: Development of the Sinuses.

MANCHESTER MEDICAL SOCIETY: SECTION OF SURGERY.—At Small Theatre, Clinical Sciences Building, York Place, 8 p.m., Mr. Alan Nicholson: Choledochoscopy.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. A. G. Leatham: Auscultation of the Heart.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Imperial Cancer Research Fund Lecture by Dr. D. J. Trevan: Some Mechanisms of Tumour Metastasis.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. S. G. Clayton: Pelvic Tuberculosis.

UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Dr. W. K. Taylor, M.Sc., Ph.D.: Communication, Control, and Memory Systems in Man and Machines.

Wednesday, January 15

B.B.C. THIRD PROGRAMME.—8 p.m., "Frontiers of Psychiatry." No. 2—Mind and Body.

●INSTITUTE FOR THE STUDY AND TREATMENT OF DELINQUENCY.—At St. George's Institute, 7.30 p.m., Dr. P. D. Scott: Adolescent Delinquent and His Family Setting.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: Biochemistry of Hormones. (2) Non-steroids.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. S. Plummer: Broncho-pulmonary Aspergillosis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. Clifford Morson: Non-tuberculous Infections of the Urinary Tract.

MIDLAND MEDICAL SOCIETY.—At Selly Oak Hospital, Birmingham, 8.15 p.m., clinical meeting.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Lock Lecture by Dr. Sheila Sherlock: Hepatic Coma.

ROYAL SOCIETY OF HEALTH, 90, Buckingham Palace Road, S.W.—2.30 p.m., Dr. W. S. C. Copeman: The Problem of Rheumatic Diseases.

WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.45 p.m., Sir Zachary Cope: Some Famous General Practitioners.

Thursday, January 16

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Dr. J. R. Mallard, Ph.D., and Dr. A. W. G. Goolden: Use of ^{131}I in Serial Tests, Double Isotope Investigations, and Normal Variations of Thyroid Function: Dr. K. E. Halnan: Advantages Obtainable from Use of ^{131}I for Thyroid Function Tests.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor G. Payling Wright: Cell Regeneration and Pathological Processes.

HILL END HOSPITAL MEDICAL SOCIETY.—8.45 p.m., Dr. H. M. C. Macaulay.

INSTITUTE OF DERMATOLOGY.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor G. Payling-Wright: Cell Regeneration and Pathological Processes.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., joint meeting with the Liverpool Paediatric Club. Symposium by Dr. A. C. Kirby, Dr. P. Pinkerton, Mr. P. P. Rickham, and Dr. T. Seager: Enuresis.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Staff House, Manchester University, 8 p.m., Dr. W. J. Glover: Some Aspects of Paediatric Anaesthesia; Dr. Elizabeth F. Hurley: Some Aspects of Thiopentone.

NORTH-EAST LONDON CLINICAL SOCIETY.—At Prince of Wales's General Hospital, Tottenham, N., 2.30 p.m., meeting.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. A. G. Leatham: Auscultation of the Heart.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Hypermetropic Patients and their Treatment.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., symposium: Onchocerciasis, to be opened by Dr. A. R. D. Adams and followed by Professor A. W. Woodruff, Mr. D. P. Choyce, Dr. F. Hawking, and Dr. W. E. Kershaw.

ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Physiology Department, Queen's College, Small's Wynd, Dundee, 5 p.m., Mr. D. J. Waterston: Emergency Surgery in the Newborn.

UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, W.C., 1.15 p.m., Professor L. S. Penrose, F.R.S.: Self-reproducing Objects.

WEST OF ENGLAND CHILD HEALTH GROUP.—At Department of Child Health Lecture Theatre, Bristol Royal Hospital for Sick Children, 8.30 p.m., Dr. D. G. Leys: A New Deal in Paediatrics.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Star and Garter Hotel, Putney Bridge, S.W., 7.30 for 8 p.m., Dr. Charles Baker and Sir Russell Brock: Surgical and Medical Advances in Cardiology.

Friday, January 17

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.45 p.m., Radiotherapy Section Meeting. Professor A. Haddow and Dr. D. A. G. Galton: Experimental Chemotherapy. Dr. H. Jackson: Effects of Radiomimetic Chemicals on Male Fertility.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. J. Wallace: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. F. H. Scadding: clinical demonstration.

INSTITUTE OF NEUROLOGY.—4.30 p.m., Sir Charles Symonds: Blindness from Cerebral Infarction.

LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.30 p.m., Round Table Discussion: Doctor-Minister Co-operation in General Practice.

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., short papers by Dr. P. A. Adam, Dr. G. D. J. Ball, Dr. D. F. Johnstone, Dr. M. R. Thomas, and Mr. H. D. S. Vellacott.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. W. B. Gabriel: Prolapse of the Rectum—Indications, Technique, and Results of Recto-sigmoidectomy and Theirach's Operation. (2) 4 p.m., Dr. D. V. Hubble: Chronic Thyroiditis.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., dissertation by Mr. M. J. McLean.

Sunday, January 19

BRITISH ASSOCIATION OF ALLERGISTS.—At Royal Society of Medicine, 11 a.m., Dr. M. Schachter: Occurrence, Properties, and Release of Kinins: 11.50 a.m., Dr. J. L. Mongar: Is Complement Needed in the Anaphylactic Reaction?; 12.40 a.m., Dr. A. B. Taylor, Miss B. J. Hayward, and Mrs. R. Augustin: Investigation of Hoigné's Light Scattering Method for the Diagnosis of Allergies; 2.30 p.m., Dr. P. Hugh-Jones: Forced Expiratory Volume as a Test for Successful Treatment of Asthma; 3.20 p.m., Dr. K. Citron: Inhalation Tests Using Pollens and Mould Spores in Allergic Asthma; 4.30 p.m., A.G.M.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At London Jewish Hospital, 10.30 a.m., clinical meeting.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Mercer.—On December 13, 1957, at Princess Royal Maternity Home, Huddersfield, Yorks, to Pamela, wife of Dr. Michael Mercer, a brother for Nigel—Nicholas William.

Robins.—On November 23, 1957, at Exeter, to Shirley (formerly Winter), and Robert Robins, a son—Michael George.

Taylor.—On September 27, 1957, at Jericho Nursing Home, Ibadan, Nigeria, to Andrée, wife of Dr. W. Norman Taylor, a daughter.

DEATHS

Banks.—On December 23, 1957, at Morena, Crieff, Perthshire, Alexander Haig Banks, M.B., Ch.B.

Beale.—On December 24, 1957, Peyton Todd Bowman Beale, F.R.C.S., of Lymore End, Milford-on-Sea, Hants., aged 94.

Boschi.—On December 23, 1957, at Chesterfield Royal Hospital, Derbyshire, Ernest James Boschi, M.R.C.S., L.R.C.P., of Staveley, Chesterfield, aged 56.

Cooke.—On December 18, 1957, the result of an accident, Michael James Cooke, M.C., M.B., B.Ch., of 9, Wensley Drive, Leeds, Yorks.

Ewart.—On December 23, 1957, at Isleworth, Middx., Francis Ewart, O.B.E., M.B., B.Ch.

Goodwin.—On December 16, 1957, Arthur Charles Goodwin, T.D., M.B., M.Ch., F.R.C.S., D.L.O., of Charlton House, Dawlish, Devon, aged 88.

Grey.—On December 12, 1957, at his home, Rodstone, Hassocks, Sussex, Sir Charles George Grey, Bt., L.S.A., late of Nigeria, aged 77.

Jackson.—On December 13, 1957, James Jackson, C.I.E., M.B., B.Ch., Major-General, I.M.S. (retired), of Little Orchard, Cofton, Starcross, Devon, aged 92.

Jenkins.—On December 12, 1957, at Cardiff Royal Infirmary, John Powell Jones Jenkins, O.B.E., T.D., M.R.C.S., L.R.C.P., of The Glebe, Panteg, Mon., aged 68.

Kramer.—On December 12, 1957, at St. Thomas's Hospital, London, S.E., Nathan Kramer, M.B., B.S.

Lea-Wilson.—On December 11, 1957, at his home, Glan-y-Mor, Laugharne, Basil Hugh Campbell Lea-Wilson, M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C. (retired), aged 72.

Medd.—On December 10, 1957, Anna Maude Seaton Medd, M.D.

Robertson.—On December 13, 1957, at 61, Falcon Avenue, Edinburgh, Stuart Dewar Robertson, M.B., Ch.B., Lieutenant-Colonel, R.A.M.C. (retired).

Smith.—On December 17, 1957, at Cheltenham, Glos, Thomas Cyril Smith, M.B., Ch.B., formerly of Gloucester.

Wood.—On December 15, 1957, in a nursing-home, Tunbridge Wells, Kent, Edward Archer Wood, M.R.C.S., L.R.C.P.

Wood.—On December 14, 1957, at Maryland, Holmscroft Road, Bettinge, Herne Bay, Kent, Stanislaus Swonnell Morton Wood, M.R.C.S., L.R.C.P., late of Station Road, Sidcup, Kent, aged 76.

Yoxall.—On December 13, 1957, at Royal Surrey County Hospital, Guildford, Surrey, Thomas Yoxall, M.R.C.S., L.R.C.P.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Anticatarrh Vaccines

Q.—*What value have parenteral anticatarrh vaccines in the treatment of chronic nasopharyngeal catarrh?*

A.—It is assumed that any obvious cause of the catarrh, such as a definite sinus infection, allergic state, or irritant like tobacco smoke or spirits, has been excluded or is being actively treated. But, even in cases without some such obvious cause, my experience is that most anticatarrh vaccines do not help very much, possibly because the catarrh is due more to irritation from allergy than infection from bacteria: occasionally the administration of a stock vaccine is followed by improvement, though these vaccines are more commonly used for prophylaxis against the secondary invaders of the common cold; and sometimes autogenous vaccines may help, though the number of patients benefiting is far outweighed by those who do not.

The failure of anticatarrh vaccines in chronic nasopharyngeal catarrh is hardly surprising. Stock vaccines contain five or six organisms, and of some of these there are large numbers of distinct antigenic types (over 70 of pneumococci, for instance), not all of which can conceivably be represented in the product. It is therefore expecting altogether too much of such a vaccine to suppose that it will produce a specific immunity to infection by these species. If such vaccines have any real effect, it is more likely to be non-specific; one can picture some benefit from giving the patient's reticulo-endothelial system a little practice in scavenging assorted bacteria of almost any kind. If any specific action is to be obtained in a case of chronic catarrh, the vaccine must clearly be autogenous. But this involves identifying the bacterial cause for the catarrh with certainty, and in practice the results are disappointing.

Inheritance of Congenital Pyloric Stenosis

Q.—*What are the present views on the hereditary factors in congenital hypertrophic pyloric stenosis? A father who had a Ramstedt's operation for this condition at the age of 7 weeks has a son who developed typical projectile vomiting and had a similar operation at the age of 4 weeks. A second son born 18 months later developed the condition, and he in turn was successfully operated on at the age of 5 weeks. All three cases were confirmed at operation by the finding of a pyloric tumour and had no further vomiting after operation. What are the chances of this condition developing in (a) any further children of this father? (b) future generations of descendants? There is no previous family history of this condition in either the father's or the mother's antecedents.*

A.—As the children successfully treated since 1920 by Ramstedt's operation come to have children of their own, it is found that a number of these children are also affected. No clear-cut hereditary mechanism is apparent, and evidence from identical twin pairs of which often only one is affected shows that children may have hereditary predisposition without being clinically affected.[1]

Initially the risk for the children of a man or woman who has recovered from hypertrophic pyloric stenosis is probably of the order of 1 in 12 for boys and 1 in 50 for girls. After one affected child has been born, the risk is probably, but not certainly, increased. In the family described, the risk for further children is somewhere between 1 in 4 and 1 in 12 for a boy, and between 1 in 16 and 1 in 60 for a girl. The initial risk for the children of the two affected sons in this family is probably 1 in 12 for a boy and 1 in 50 for a girl.

REFERENCE

[1] Carter, C. O., and Powell, B. W., 1954, *Lancet*, **1**, 746.

Pulmonary Tuberculosis in Radiologist

Q.—*A doctor attending a course in radiology was found to have bilateral pulmonary tuberculosis. Resolution was slow, but after 18 months off work he has now resumed his course. While in hospital he had six sets of tomograms besides numerous plain x-ray films and an intravenous pyelogram. (1) Is there any contraindication to him carrying out fluoroscopy in view of the amount of radiation he has already received? (2) Would being a radiologist carry any increased risk of reactivation of his phthisis?*

A.—It is impossible to calculate the amount of radiation received by this doctor during his six tomographic examinations, his numerous plain films, and his intravenous pyelogram. Techniques vary widely from hospital to hospital; the dose received at tomography is especially variable, because the use of a multi-layer cassette may reduce the dose to rather less than a half of that received when single cassettes are used. The important factor in this case, therefore, is to consider how low a dosage rate he could achieve in the course of his work as a radiologist. Provided he wears an adequate double-sided lead rubber apron covering not only the front but also the back of his body, no appreciable amount of radiation should reach his bones, and therefore the danger of leukaemia should be very slight and to all intents and purposes no greater than if he were to follow some other occupation. Such lead rubber aprons also protect the gonads.

There is no evidence of an increased risk of his phthisis being reactivated by the amount of radiation which a radiologist commonly receives in the course of his work.

Crying Fits

Q.—*An otherwise healthy boy aged 2 has for the last year had occasional epileptiform attacks of the following pattern: After a slight knock, often on the head, he starts crying; his eyes then roll up, his head goes back, his body becomes stiff, and he appears unconscious for a few seconds. Following this there is no clonus but he goes limp and remains pale for up to an hour. What is the cause of these attacks? How should they be treated and what is the prognosis?*

A.—The attacks described are not epileptic in the ordinary sense. They happen because of embarrassment of the cerebral circulation caused by thoracic stasis during the period of crying. Obstruction to the return of venous blood is severe enough to prevent proper filling of the left heart and there is consequent cerebral ischaemia. In these circumstances consciousness may be lost and an actual convulsion take place. The child need not be given phenobarbitone or other anticonvulsants, and the attacks will not do any permanent harm. Sometimes children get into the habit of prolonged crying, but firm handling can terminate a paroxysm and teach a child to behave with more control. I have never found this condition lasting beyond the first few years of life.

Dietary Restriction in Infective Hepatitis

Q.—*To what extent is it necessary to modify the diet during and after an attack of infective hepatitis, and for how long?*

A.—The traditional low fat, high carbohydrate diet is popular not because of any intrinsic value but rather because it has proved the most palatable to the anorexic patient. Apart from this, no benefit occurs from the rigid insistence upon a low fat diet. In fact a controlled dietetic study has revealed the reverse. The patients receiving a high fat diet regained their weight more rapidly and liver function tests returned to normal sooner.[1] The favourable result may be attributed to the larger number of calories in the high fat diet.

When appetite returns, high protein intake may hasten recovery. Excess protein, however, is harmful to the

severely ill patient in impending hepatic coma. The food should always be the most appetizing for the patient. Supplementary amino-acids and lipotropic agents have not proved of definite value. Unusual exertion must be avoided for six months after hepatitis, and alcohol should be denied for six months and preferably for one year after recovery. The patient often has little inclination for it, and excessive consumption undoubtedly leads to relapses.

REFERENCE

1 Hoagland, C. L., Labby, D. H., Kunkel, H. G., and Shank, R. E., *Amer. J. publ. Hlth*, 1946, **36**, 1287.

Oral Penicillin V and G Compared

Q.—*What are the comparative advantages and disadvantages of penicillin V and penicillin G for oral therapy? In what form is it best to administer them?*

A.—The advantage of penicillin V is that it is acid-resistant and therefore passes through the stomach unchanged. Penicillin G undergoes a variable degree of destruction, and the amount absorbed consequently varies and is sometimes considerably less. The proportion of a dose of penicillin V which is excreted in the urine is constant at about 25% : that of penicillin G may occasionally be as high as this but is more often lower and sometimes as low as 10%. The only evident disadvantage of penicillin V is that it is slightly less active against some strains of streptococci, pneumococci, and certain Gram-negative organisms ; on the other hand, when there is a difference in activity against staphylococci, penicillin V is the more active of the two. These differences in sensitivity are usually less than twofold, and could be compensated for when unfavourable by a moderate increase in dose.

Penicillins G and V are both obtainable in the form of tablets, or suspensions in a non-aqueous vehicle ; there are also preparations of penicillin V in capsules. It probably matters very little in what form penicillin V is taken ; the absorption of G may be slightly improved if the preparation includes a buffer, although this is less important in favouring absorption than the time of administration, which should be before meals.

Halitosis and Fats

Q.—*In those with no evidence of infection in the mouth or respiratory tract, may periodical attacks of halitosis be due to delayed emptying of the stomach, as perhaps after a fatty meal? If so, what treatment is advised for such cases?*

A.—There is a clear-cut relation between fat in the diet and halitosis. It does not seem to be a question of gastric stasis, for the symptoms may persist long after the stomach is empty. It is due probably to the production of volatile fatty acids in the intestine, their absorption into the blood stream, and excretion into the lungs. A low fat diet often greatly improves the condition.

Rationale of Shock Treatment

Q.—*What is the rationale of shock treatment in the psychoses?*

A.—There are 20 or more theories of how modern shock therapies work in the treatment of the psychoses. Most are, however, only theories, and it is very doubtful if we yet have the right answer simply because we know so little about how the brain really works. It is important, however, to realize that electric shock treatment works only if a full cerebral epileptic fit is given (although there is no need for any concomitant epileptic bodily movements, which can now be abolished by the use of suxamethonium). Likewise the best results from insulin-coma treatment generally occur when really deep comas are given, and the effects of insulin-coma are often enhanced by the giving of convulsions in the early coma period.

Any theory, therefore, trying to provide a rationale of shock treatment must explain why only a full fit or a very deep coma is usually effective. Many physiological and psychological theories fall down in trying to explain these facts. It does appear, however, that the effects of most shock therapies are to disrupt certain types of recently implanted behaviour and thought patterns. Thus the longer abnormal thoughts and patterns have been present in the brain the less amenable they are generally to shock treatments. The effect of electric shock treatment in depression also suggests that convulsions do have some specific action on the abnormal inhibitory processes affecting brain function in depressive states. Much further research, however, will be necessary before we know how shock treatments really work. The important thing is that they do often work so very well indeed in the selected patient. We must remember that it took hundreds of years to find out why quinine was so effective in malaria, and that we do not even yet know how insulin really works.

Acute Salicylate Poisoning

Q.—*In a recent annotation the essential metabolic effect of large doses of salicylates was stated to be the production of a respiratory alkalosis.[1] Textbooks, however, when discussing the treatment of acute salicylate poisoning, usually recommend intravenous sodium bicarbonate or sodium lactate to combat a supposed metabolic acidosis, which is said to be the usual cause of death. Is this still regarded as the best treatment?*

A.—Salicylate is primarily a metabolic stimulant, and the breathlessness observed when large doses are given is a manifestation of the greatly increased oxygen consumption. In acute poisoning cases it may be severe and may be associated with hyperpyrexia, though collapse often supervenes. The keynote of treatment of salicylate poisoning is elimination of the drug as quickly as possible, and to this end sodium bicarbonate may be given by mouth or intravenously to hasten renal excretion of the drug. The metabolic stimulation should be allowed to run its course, and active measures taken to promote heat loss and so avoid hyperpyrexia ; additional fuel in the form of glucose will prevent starvation ketosis. Interference with respiration in an attempt to control breathlessness is contraindicated. Circulatory collapse is a grave development and is treated in the usual way.

REFERENCE

1 *Brit. med. J.*, 1957, **2**, 812.

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